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Further Consideration of the Cushing Syndrome[1]

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FOR several years we have endeavored to follow the reported cases of the Cushing syndrome. In many instances, by correspondence with the physician, it has been possible to pursue a suspected case to verification, and to obtain sections of the pituitary gland to compare with others in the collection of the Brain Tumor Registry. Prior to this present war we received data from most of the authors of case reports save those who had been dislocated from their practices. The war and other duties have prevented us from completing a full report on this material, yet certain impressions that were gained perhaps deserve to be presented in an informal way at this time.

A recently verified case of the Cushing syndrome reported by Paschkis, *et al.* (26) serves to illustrate the unsolved problem of this disease. The patient, Miss E. R., was a beautiful girl of 17 when the syndrome began to be active, and the first signs were the development of a moon-face, acne, a tendency to baldness, fatigability, and amenorrhea. Soon after the onset we had the fortune to see the patient, who had been referred to Dr. Cushing by Dr. Paschkis and his associates. She was regarded as a 'suspect' solely on the grounds of the general physical appearance, for the clinical studies revealed only a minimal amount of decalcification of the vertebrae and no other positive findings. She received adequate roentgen-ray therapy to the pituitary region early in the disease, and there appeared to be a transient remission of the symptoms following one of the courses of radiation given during a series of injections of estrogenic hormone. Soon, however, there was a re-activation of the disease, which progressed to fatality after a long and miserable period of hypertension, mental depression and spontaneous fractures. The fatality was precipitated by sepsis spreading from a furuncle of the cheek.

The several pneumograms of the adrenal glands were unsatisfactory because of the patient's adiposity, but were interpreted as showing no discrete tumor. At autopsy the

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adrenals were found to be bilaterally hypertrophied with small 'Knötchen,' but without sizable tumor. There was no tumor of any other endocrine gland to be found, but the Crooke changes were present in the basophilic cells of the anterior lobe of the pituitary. The patient had not had adequate therapy with androgen as suggested by Albright (2). The progressive, unremitting character of the disease in view of the paucity of pathological findings in the endocrine glands, the hypertrophied adrenals and the Crooke changes being the only positive findings, was remarkable.

In 1940 we had assembled 98 cases with autopsy findings and clinical records sufficiently clear to warrant inclusion as probable examples of the syndrome as described by Cushing. Perhaps more than 25 additional cases have been added since 1940, but the figures compiled at that time[2] serve to illustrate the trends of the data. The 98 cases, in 63 of which we were permitted to examine the pituitary body, comprised the basis for the data in table 1.

TABLE 1. AUTOPSIED CASES OF CUSHING SYNDROME TO 1940

Association with Tumor	Total No. of Cases	Personal Examination of Pituitary	
		No. of cases	No. of cases with Crooke change
Pituitary adenoma	60	39	35
Adrenal tumor	22	11	11
Thymic tumor	3	3	3
Arrhenoblastoma	1	1	1
No tumor of any gland	12	9	8
Total	98	63	58

Among the 39 pituitary adenomas personally examined 33 were basophilic, including 5 of transitional type; 2 were chromophobe, 2 were mixed, 1 was malignant with metastases, and 1 unclassified. Of the 21 that we were unable to examine, 16 were reported as basophilic, 1 eosinophilic, 1 chromophobe, 2 were claimed to be fibroadenomas, and 1 was a malignant adenoma. The microscopical conglomerations that have sometimes been called adenomas were excluded from those listed above.

Crooke (12) described a peculiar hyalinization of the basophilic cells of the anterior lobe apart from any tumor that may have been present, and suggested that this change might have some etiological bearing upon the disorder. In the 63 pituitaries that we examined, the Crooke change was present in 58, as shown in table 1. The 5 cases in which the Crooke change was absent, 4 with pituitary adenoma and 1 without tumor of any gland, were found on later review to be not wholly satisfactory clinical examples of the syndrome.

In the group of 22 verified instances of the syndrome associated with adrenal tumor, there were 6 benign and 16 malignant growths. Only 2 of the patients were males. Hypertrophy of the clitoris has been mentioned as a possible sign of adrenal tumor, reflecting the virilizing effect of the hormonal disturbance. The clinical reports of the 20 females mentioned the clitoris as hypertrophied in 5, normal in 5, smaller than normal in 1, and omitted reference to it in 9.

Two cases of arrhenoblastoma said to have simulated the Cushing syndrome deserve special consideration because of the difficulty, already expressed in the reports by Norris (25) and by Canelo and Lisser (8), of determining histologically the parentage of the ovarian tumor cells. Considering the clinical courses in the light of the pathological findings, we are inclined to interpret the Canelo-Lisser case, in which there was no Crooke change in the basophilic cells, as fairly representative of the known examples of arrhenoblastoma, while the Norris case, in which hyalinization of the basophilic cells was marked, approximates the Cushing syndrome. Neither is a perfectly typical example of the syndrome to which we have assigned it. They appear to represent variants of what we are inclined to call borderline cases.

In reviewing the groups with adrenal involvement we were impressed by the fact that there were borderline examples where virilism shaded over into the Cushing syndrome, making a differentiation between the two quite difficult from the data available in the written reports. It was not uncommon for the patients with virilism to have glycosuria or hyperten-

[2] This material was presented in part at the Third International Cancer Congress, Atlantic City, New Jersey, September 15, 1939.

sion, and in not one of these pituitaries we examined was there hyalinization of the basophilic cells of the anterior lobe. However, the patients with the true Cushing syndrome also had decalcification of the bones, the typical moon-face, amenorrhea and mental depression with less marked characteristics of true virilism in their external appearance, and the Crooke change in the basophiles was usually present.

In the European literature a syndrome associated with malignant tumor of the adrenal cortex, virilism and adiposity has been described under variations of the term Cooke-Apert-Gallais syndrome (11, 6, 18). Certain of these cases (10, 19) probably represent examples of the Cushing syndrome.

The outcome of the patients with adrenal tumor that were subjected to operation for extirpation of the growth was highly interesting. In those cases of true virilism in which the tumor was operable, satisfactory recovery was the rule. However, in the 22 cases of adrenal tumor with the Cushing syndrome all 18 patients who underwent operation died in the immediate post-operative period of shock resembling adrenal insufficiency. One of these was thought to have no adrenal on the opposite side, but the notes do not exclude the possibility that a tiny atrophic gland may have been missed in the extensive perirenal fat. A few of the fatalities occurred in spite of fairly adequate measures to combat adrenal insufficiency. It is safe to say, however, that in none of the cases reviewed prior to 1940 was there optimum treatment for adrenal insufficiency.

In contrast to this may be mentioned the relatively favorable outcome of surgical attack on the pituitary body. In two cases of the Cushing syndrome, Pattison inserted radon seeds into the sella turcica after excluding the possibility of an adrenal tumor (27). From one of these patients, fragments of the anterior lobe were removed, verifying the presence of the Crooke change. Pattison later wrote that he had operated upon another patient and had partially removed a basophilic adenoma of the pituitary and implanted radon seeds. The patient unfortunately succumbed to a Ludwig's angina on the fifth post-operative day in spite of vigilant therapy. We had the opportunity of personally examining sections of the adenoma and also of the anterior lobe, in which the Crooke change was marked.

The recent demonstration by Albright, *et al.* (2) of a nitrogen imbalance in the patients afflicted with the Cushing syndrome has aroused much interest. Dr. Cushing was inclined to ascribe considerable importance to an unusual loss of nitrogen which was discovered in the case of Dr. E. G. F. by Professor Woodyatt (Cushing: Case 11, ref. 14). The patient had been studied by Professor Woodyatt at intervals and was the subject of much correspondence. At this time Dr. Cushing was formulating his views about the disorder, and, as expressed in his many letters to Dr. Woodyatt, they appear to be prophetic of the things later verified. However, it was Dr. Woodyatt who first noted the excessive nitrogen loss which is probably best described in his own words written January 18, 1932:

> One of the things that specially interested me in his case was the enormous protein metabolism which he showed during certain periods, making it technically difficult to maintain him in nitrogen balance. Have you found in the literature descriptions of this feature in similar cases? Then there was the flush and the leucocytosis. The polyuria would seem to be adequately explained by the magnitude of the urea excretion. I will be much interested to know what you have in mind about the nature of his trouble . . . .

Dr. Cushing replied:

> The long and short of it is that he represents a type of what I think is basophilic hyperpituitarism . . . .

On March 10, 1932, Dr. Woodyatt wrote:

> Our data show that the increased output of nitrogen was due to an increase of all the urinary nitrogenous substances in the proportions in which they occur in health. The great bulk of the urinary nitrogen was urea nitrogen (85 to 90%). (Dr. Woodyatt did not send the exact data.) . . . . The azoturia was a discovery of my own. I believe it has not been recorded in such a case (?) and that it may be of considerable theoretical interest. As the total metabolic rate was normal, the excess of nitrogen in the urine due in the main to an excess of urea, and as the nitrogen partition was otherwise normal, we may speak of an increased protein catabolism . . . . The traffic in urea was sufficient to account for the polyuria, and this offers a possible and quite plausible explanation of that symptom.

This letter arrived too late for Dr. Cushing to include in the manuscript of the paper originally published in the Bulletin of the Johns Hopkins Hospital (14), but reference was made to it in a reprinting (p. 146, ref. 15). On March 12, 1932 he wrote to Dr. Woodyatt:

> I wish I had known that this azoturia business was your own discovery . . . . I am sending on a copy of Teel and Watkins' paper in which they showed that there was marked retention of nonprotein nitrogen in experimental acromegaly. Do take the matter in hand . . . .

Here the correspondence ended because the patient had a recrudescence of symptoms and died suddenly of cerebral hemorrhage.

The problem remained for Albright and coworkers to take advantage of. In 1941 (2) they reported that in 3 patients with the syndrome a striking retention of nitrogen was induced by injections of testosterone. Progesterone had the same effect to a slight degree, but estradiol benzoate had no effect. The testosterone also induced a marked increment in the calcium balance. The beneficial effects of the testosterone, which apparently caused a remission of syndrome, in one case lasted for months after the treatment was stopped. Recently Albright has stated (1) that on further study the majority of his patients have been on the borderline of nitrogen balance, rather than in actual deficit. He has called attention to some of the resemblances between the Cushing syndrome and the 'alarm reaction' of Selye, and has formulated an interesting set of theories relating to the metabolic disturbances.

We have gained the impression that most investigators have tended to attribute the polyphagia and polydipsia to the glycosuria. This supposition may have to be revised, for glycosuria may be absent at the onset or even in the later stages of the disease. This was true in the patient Dr. E. G. F., as recorded in a recent letter from Dr. Woodyatt:

> It seems that he gained weight and had polyuria prior to the discovery of glycosuria, and later polyuria and azoturia without sugar in the urine.

These interesting studies on nitrogen metabolism need amplification, and probably until more data are available, we should not make too much of them. However, we have noted in the records of certain patients their extraordinary desire to eat meat, sometimes raw meat. There is one striking example (Menzel: Case I, ref. 24) in which at the onset of the disease the young man was found daily at the slaughter house eating quantities of raw meat, most often liver. There are others who have been enormous meat-eaters. One patient (Cushing: Mr. LaF. ref. 16), on the other hand, developed the disease in prison after several weeks of solitary confinement on a diet of only bread and water. His first symptoms of hyperthyroidism were sufficient to lead to a subtotal thyroidectomy, but the full syndrome rapidly developed. In another case as yet unverified, reported from Algiers just prior to the war (9), the syndrome appeared during pernicious vomiting of pregnancy, and it progressed to an extreme degree, when spontaneous abortion occurred followed by a complete remission. The whole process was repeated with the next pregnancy and again a remission occurred. We might speculate on whether the 'alarm reaction' of Selye, mentioned by Albright, had anything to do with precipitating the disease in these patients. Now that attention has been directed to the probable significance of the disordered protein metabolism and of abnormal diets, it is hoped that future case reports will make some special mention of these points. One would like to know whether these patients select protein food by preference, like Richter's (28, 29) experimentally pancreatiectomized and other deficient animals which, when given their choice of foods, select the items that supply their metabolic wants.

The first symptoms of the disease to be noted are usually (*a*) a change in appearance, particularly a tendency to develop a moon-face, most striking in the women; (*b*) polyphagia and adiposity in both men and women, and (*c*) in the women, amenorrhea, and in men, a failure of the libido. In those patients with great polyphagia and polydipsia, the disease appears particularly relentless and progresses rapidly.

The problem has been complicated by our gradual realization of the fact that this syndrome can occur without tumor of any endocrine gland. Dr. Cushing believed that the cases with pituitary adenoma could be explained on the basis of the adenoma's secre-

tion stimulating the adrenals and parathyroids and gonads in an unrestrained way, with a notable absence of the growth or thyrotropic actions. But Albright, *et al.*, have pointed out that the bone disorder seen in hyperparathyroidism (osteitis fibrosa generalisata) is not that seen in Cushing's syndrome (osteoporosis). They suggest that the osteoporosis in Cushing's syndrome is due to failure to lay down bone matrix as a result of the disordered protein metabolism (2, 3). The clinical histories reveal that the disease in many instances began with hyperthyroidism or the development of goiter, and almost half of the patients have had elevated basal metabolic rates. One cannot assume, therefore, that the thyrotropic hormone is deficient. The position of the growth hormone is not clear, but presumably, because of the wastage of nitrogen, it is relatively deficient.

These facts, together with the substantial number of cases in which the syndrome has been associated with a primary adrenal tumor, lead to the tentative conclusion that the basic disorder is an excess of adrenal cortical function with an altered pattern of secretion of the patient's own hypophysis. Certain evidence, which needs to be amplified, is available to show that this is true; for example, Tepperman and Engel (32) have noted increased protein catabolism as the 'basic metabolic theme' in their list of causes of hypertrophy of the adrenal cortex in experimental animals, such as over-consumption of protein, starvation, and pregnancy. There have been reports of an increased excretion of cortin (35, 36) and high urinary values for the 17-ketosteroids (13, 17). Abnormal amounts of cortin in the serum have also been observed (4, 5). Further, in these patients there have been electrolyte disturbances somewhat the opposite of those in adrenal insufficiency. Yet although these trends in the data are very interesting and perhaps highly significant, they are nevertheless so confusing, as shown by the reviews of Loeb (22) and Kepler and Keating (21), that further observations on the electrolyte balance will be required to differentiate clearly the patterns of the various syndromes.

In the cases of the syndrome with adrenal tumor the hyalinization of the anterior lobe basophiles is striking and therefore the Crooke change probably does not represent the source of adrenal over-function when there is no tumor of any gland. Were the Crooke change the source, one would not expect the high mortality rate, apparently from adrenal insufficiency, following operative excision of adenomas, the opposite adrenal invariably being atrophic.

In formulating any program for therapy, one must first determine whether there is a true tumor of the adrenal. If one is found there seems no other alternative than to extirpate it because most of these tumors are malignant and ultimately metastasize. It may be that the safest treatment would be some form of graded radiation therapy directed at the tumor preoperatively, as is the practice in dealing with certain renal growths. The growth then may shrink, with an amelioration of symptoms, and it is conceivable that in the meantime the opposite adrenal may resume function so that surgical excision of the tumor would not lead to such severe withdrawal symptoms. This suggestion is offered without our having had the opportunity to put it to a test, nor are we aware of the method's having been tried elsewhere.

Once adrenal tumor and also thymic tumor were ruled out, the decision would have to be made as to whether operative or radiation therapy should be directed at the pituitary body. Any structural changes in the sella turcica and its neighborhood would naturally lead one to suspect tumor, but such changes were observed in only 2 of the 60 verified cases of pituitary adenoma. There are on record two striking instances of complete remission of the disease following radiation of the hypophysis. Cushing's patient, Alice D. (Case 15, ref. 15), had an extraordinary remission which has lasted more than 11 years. Jamin's patient (20) was a boy of 14 with all the signs of the syndrome, who completely recovered following radiation therapy of the hypophysis. Several years later while in military service he was fatally injured, and fortunately the pathologist secured the hypophysis for Dr. Cushing. There were no physical abnormalities found, and in particular no tumor was present in any endocrine gland. We have examined the sec-

tions of the anterior lobe, and after considerable search could detect signs of the Crooke change in only a very few cells. Temporary improvement following radiation therapy has been observed, as in Cushing's patient, Dr. E. G. F., and Paschkis' patient, Miss E. R.

The aforementioned Cushing's Alice D. and Jamin's case conceivably may have been examples of spontaneous remission like Cushing's Minnie G. (Case 1, ref. 14), who received no therapy and has remained reasonably well for over 20 years. These may all belong to the group without tumor, for should radiation of a pituitary adenoma cause a period of remission, one might expect this to be followed by reactivation as in some instances of acidophilic adenoma with acromegaly. The type of pituitary tumor may have some bearing on the sensitivity to radiation. It may be noted that of the 60 pituitary adenomas in cases of the syndrome, although the majority were basophilic, a few were composed of other types of cells.

Roentgen treatment, however, has failed in the majority of cases, and it would seem that, if one well-planned course of radiation or testosterone were unsuccessful, a neurosurgical approach with an exploration of the gland and excision of an adenoma might be advisable even at the expense of a subtotal hypophysectomy. A basophilic adenoma is often marginal, and sizable enough to see.

Any method that can be devised to improve the patient's condition pre-operatively would be highly desirable, for there are a number of unusual hazards in addition to the late complication of adrenal insufficiency already mentioned in the cases with adrenal tumors. There is a tendency to succumb to infections which arise from trivial causes; many of the deaths from infection originated in pin pricks, retrograde pyelography, and even well-performed operative procedures, both adrenal and intracranial. Further, in advanced stages the extremely fragile bones may be fractured on lifting the patients from bed to X-ray or operating table. Hypertension may also be a technical hazard in a transfrontal exploration of the pituitary body.

Any theories proposed on the etiology of the syndrome should in some way give consideration to the hypertensive cardio-vascular renal disease which so commonly leads to fatality. Although sepsis perhaps heads the list as the immediate cause of death, 17 of the 58 patients with pituitary tumors previously reported (16) died of congestive failure, apoplexy or uremia. In this group 29 had systolic pressures of 200 mm. of Hg or over, and 35 had diastolic pressures of 120 mm. of Hg or over. In many cases the values recorded in a normal range are misleading because the first readings were made in a terminal phase of the disease, when cardiac failure, advanced sepsis, or some other complication presumably lowered them. A start in this direction would seem to be that of Barnett, Perley and Heinbecker (7), who have collected some new evidence which shows that a humoral agent affecting kidney function is secreted by the eosinophilic cells.

Another complication not uncommon is a mental depression amounting to a serious psychosis. There were 3 suicidal deaths in the 58 verified cases with pituitary adenoma previously reported (16), and we have learned of others in recent cases. The mental depression of Miss E. R. of Paschkis, *et al.* (26) could have been explained by her unhappiness with her physical appearance which she contrasted with her sister's beauty, a daily reminder of her dreadful condition. The suicidal tendencies are real dangers, but whether the mental reactions represent more than a normal response to the patient's physical change and usually hopeless future remains to be determined. One cannot assume without further study that the endocrine disturbance produces a basic alteration of special brain functions. Psychiatric observations along these lines, such as those by Maclay and Stokes (23), might profitably be amplified in future cases.

The striking plethora which is a feature of a rapidly progressing case also calls for explanation. An erythrocytosis has been observed in nearly half of the patients, but there is uncertainty as to whether this is a primary effect of the disease or secondary to some terminal complication, such as dehydration, or passive congestion. We are inclined to agree with Dr. Cushing's original conception that plethora and erythrocytosis are important basic reactions in the advancing syndrome, but further data

on erythrocyte count, cell volume and blood volume at different stages in the disease are necessary before a final opinion can be reached.

With the accumulation of verified cases in which adequate roentgenological studies are available, it might be possible on re-examinng the films to differentiate the osteoporosis associated with nutritional and post-menopausal states from that of the Cushing syndrome. In this connection it will be of interest to learn whether the bilateral callus-like changes near the costochondral junctions, usually in the lower ribs, described by Sussman and Copleman (31) will prove to be characteristic of the Cushing syndrome.

Further efforts toward the experimental reproduction of the syndrome in animals are clearly indicated. Early attempts with pituitary extracts were hampered by the development in the animals of antihormones to the adrenotropic and other pituitary hormones because the preparations used were crude and contained antigenic material (33, 34). We do not yet know whether pure adrenotropic hormone is antigenic in a foreign species, but await with great interest reports on the effects of long-continued injections of this hormone. Possibly one might profitably study the immunological properties of the patient's blood serum toward pituitary hormones, for it will be recalled that the only success with the experimental reproduction of the Crooke change has been by the injection of an animal with an antihormone serum (30). Heinbecker[3] opened still another approach to the problem when he reported changes in the hypothalamus in 4 of 6 cases of the syndrome without tumor of any gland. In serial sections he noted atrophy of the nuclei of the hypothalamus, particularly the paraventricular nuclei.

Whatever lines of investigation are pursued in our efforts to determine the etiology of the disorder we may profitably recall the historical situation as it existed with acromegaly. The adrenal hyperplasia, often associated with small cortical tumors, that occurs in acromegaly is far more than it is in the Cushing syndrome, and there also is a striking hypertrophy of the thymus. Therefore each of these glands has been considered as the basic factor in acromegaly. Yet, fortunately, the experimental reproduction of the disease with pituitary extracts in dogs focused attention on the pituitary.

There is a tendency for physicians to report unverified cases of the Cushing syndrome ascribing benefits from some special therapy, without the clinical and laboratory data that are so important to an understanding of the disease. An editorial board of a journal undoubtedly is perplexed as to what policy to adopt toward such reports. We believe that case studies should be published and all data included. Care should be taken to avoid premature publication, because the disease progresses so that in not too many months either the success of treatment will be apparent or it may be possible to verify the diagnosis.

[3] Presented at the meeting of the American College of Surgeons in Boston, 1941.

REFERENCES

1. ALBRIGHT, F.: Cushing's syndrome. Its pathological physiology, its relationship to the adrenogenital syndrome, and its connection with the problem of the reaction of the body to injurious agents ("alarm reaction" of Selye). *Harvey Lect.* 1943 (in press).
2. ALBRIGHT, F., W. PARSON AND E. BLOOMBERG: Cushing's syndrome interpreted as hyperadrenocorticism leading to hypergluconeogenesis: results of treatment with testosterone propionate. *J. Clin. Endocrinol.* 1: 375. 1941.
3. ALBRIGHT, F., P. H. SMITH AND A. M. RICHARDSON: Postmenopausal osteoporosis. Its clinical features. *J. Am. Med. Ass.* 116: 2465, 1941.
4. ANDERSON, E., AND W. HAYMAKER: Cushing syndrome; adrenal cortical hormone (cortin) in blood and urine of patients. *Proc. Soc. Exper. Biol. & Med.* 38: 610. 1938.
5. ANDERSON, E., W. HAYMAKER AND M. JOSEPH: Hormone and electrolyte studies of patients with hyperadrenocortical syndrome (Cushing's syndrome). *Endocrinology* 23: 398. 1938.
6. APERT, E.: Dystrophies variées (Hermaphrodism, puberté précoce, hirsutisme, obésité) en coincidence avec des lésions des capsules surrénales. *Bull. Med., Paris* 24: 1161. 1910.
7. BARNETT, H. L., A. M. PERLEY AND P. HEINBECKER: Influence of eosinophile cells of hypophysis on kidney function. *Proc. Soc. Exp. Biol. & Med.* 52: 114. 1943.
8. CANELO, C. K., AND H. LISSER: A case of arrhenoblastoma which simulated Cushing's disease. *Endocrinology* 24: 838. 1939.
9. COHEN, V.: Un cas de maladie de Cushing ou adénome basophyle de l'hypophyse. Ses rapports avec la grossesse. *Tunisie méd.* 31: 76. 1937.
10. COMBY, J.: Hirsutisme et syndrome de Cushing. *Arch. de méd. d. enf.* 40: 173. 1937.

11. COOKE, W.: A case of hydrocephalus internus. *Med.-Chir. Trans.* 2: 17. 1811.
12. CROOKE, A. C.: A change in the basophil cells of the pituitary gland common to conditions which exhibit the syndrome attributed to basophil adenoma. *J. Path. & Bact.* 41: 339. 1935.
13. CROOKE, A. C., AND R. K. CALLOW: The differential diagnosis of forms of basophilism (Cushing's syndrome), particularly by the estimation of urinary androgens. *Quart. J. Med.* n.s. 8: 233. 1939.
14. CUSHING, H.: The basophil adenomas of the pituitary body and their clinical manifestations (pituitary basophilism). *Johns Hopkins Hosp. Bull.* 50: 137. 1932.
15. CUSHING, H.: Papers relating to the pituitary body, hypothalamus and parasympathetic nervous system. Springfield, Ill.: Charles C Thomas, 1932.
16. EISENHARDT, L., AND K. W. THOMPSON: A brief consideration of the present status of so-called pituitary basophilism. *Yale J. Biol. & Med.* 11: 507. 1939.
17. FRASER, R. W., A. P. FORBES, F. ALBRIGHT, H. SULKOWITCH AND E. C. REIFENSTEIN, JR.: Colorimetric assay of 17-ketosteroids in urine. *J. Clin. Endocrinol.* 1: 234. 1941.
18. GALLAIS, A.: Diagnostic anatomo-clinique du syndrome génito-surrénal. *Rev. Gynecol. Chir. abdom.* 22: 1. 1914.
19. GUINON, L., AND BIJON: Déviation du type sexuel chez une jeune fille, caractérisé par l'obésité et le développement d'attributs masculins simulant l'hermaphrodisme. *Bull. Soc. Péd., Paris* 8: 129. 1906.
20. JAMIN, F.: Die hypophysäre Plethora. (Cushingsche Krankheit: pituitary basophilism). *Münch. med. Wschr.* 81: 1045; 1085. 1934.
21. KEPLER, E. J., AND F. R. KEATING: Diseases of the adrenal glands. II. Tumors of the adrenal cortex, diseases of the adrenal medulla and allied disturbances. *Arch. int. med.* 68: 1010. 1941.
22. LOEB, R. F.: The adrenal cortex and electrolyte behavior. *Bull N. Y. Acad. Med.*, 2nd series 18: 263. 1942.
23. MACLAY, W. S., AND A. B. STOKES: Mental disorder in Cushing's syndrome. *J. Neurol. & Psychiat.* 1: 110. 1938.
24. MENZEL, W.: Zur Pathogenese der Cushingschen Krankheit. *Ztschr. f. klin. Med.* 131: 565. 1937.
25. NORRIS, E. H.: Arrhenoblastoma. A malignant ovarian tumor associated with endocrinological effects. *Amer. J. Cancer* 32: 1. 1938.
26. PASCHKIS, K. E., P. A. HERBUT, A. E. RAKOFF AND CANTAROW: A case of Cushing's syndrome with adrenal cortical hyperplasia without pituitary basophilism. *J. Clin. Endocrinol.* 3: 212. 1943.
27. PATTISON, A. R. D., AND W. G. A. SWAN: Surgical treatment of pituitary basophilism. *Lancet* 1: 1265. 1938.
28. RICHTER, C. P., AND J. F. ECKERT: Increased calcium appetite of parathyroidectomized rats. *Endocrinology* 21: 50. 1937.
29. RICHTER, C. P., AND C. H. SCHMIDT, JR.: Behavior and anatomical changes produced in rats by pancreatectomy. *Endocrinology* 25: 698. 1939.
30. SEVERINGHAUS, A. E., AND K. W. THOMPSON: Cytological changes induced in the hypophysis by the prolonged administration of pituitary extract. *Amer. J. Path.* 15: 391. 1939.
31. SUSSMAN, M. L., AND B. COPLEMAN: The roentgenographic appearance of the bones in Cushing's syndrome. *Radiology* 39: 288. 1942.
32. TEPPERMAN, J., AND F. L. ENGEL: Metabolic determinants of adrenal size and function. A review of adrenal cortical hypertrophy. [New York: Privately printed for the Josiah Macy, Jr. Foundation, 1942.] *Endocrinology* 32. 373. 1943.
33. THOMPSON, K. W., AND H. CUSHING: Experimental pituitary basophilism. *Proc. Roy. Soc. London, series B.* 115: 88. 1934.
34. THOMPSON, K. W., AND H. CUSHING: Inhibition of action of pituitary hormones by animal sera. *Proc. Roy. Soc. London, series B.* 121: 501. 1937.
35. WEIL, P. G., AND J. S. L. BROWNE: The excretion of cortin after surgical operation. *Science* 90: 445. 1939.
36. WEIL, P. G., AND J. S. L. BROWNE: The excretion of cortin under conditions of damage. *J. Clin. Invest.* 19: 772. 1940.

Oral Therapy with Sodium Estrone Sulfate. I. Induction of Bleeding and Cycle Regulation in Functional Amenorrhea[1]

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Successful oral treatment of climacteric symptomatology with a commercial preparation[2] containing sodium estrone sulfate has been reported (1–4). The source of this conjugated, water soluble, natural estrogen is urine of pregnant mares and it is available commercially in the form of tablets, each of which contains 1.25 mg. of the conjugated estrogen, expressed as sodium estrone sulfate. Previous clinical studies have indicated that it is far more active by mouth than other natural estrogens or their derivatives and that, when administered orally, its effectiveness compares favorably with that of synthetic diethylstilbestrol.

In view of these facts, we have employed two objective clinical applications of estrogens to assay the effectiveness of sodium estrone sulfate: *a*) the induction of bleeding and cycle regulation in functional amenorrhea; and *b*) the induction of hemostasis and cycle regulation in functional uterine hemorrhage. Since factual data are available with regard to the effectiveness of oral therapy with diethylstilbestrol in these applications, comparison of the relative potencies of sodium estrone sulfate and diethylstilbestrol is possible. The present communication reports our results of the first of these clinical applications. A subsequent report will detail results of the second application.

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[2] Premarin, supplied by Ayerst, McKenna and Harrison, Ltd., Montreal, Canada.

DATA

Eighteen amenorrheic women, whose ages ranged from 14.5 to 38 years, were treated. Seven had not experienced menarchal bleeding; 7 had not bled for 8 months or longer; and 4 bled infrequently. Diagnostic studies related the non-occurrence of bleeding in all cases to spontaneous functional disturbances.

Sodium estrone sulfate was given orally and cyclically. From 2.5 to 15.0 mg. were administered daily for 20 consecutive days. There was permitted to follow an interval without treatment usually of 10 days' duration. When hormone-withdrawal bleeding occurred, further series of therapy were given for cycle regulation; these were initiated 5 days following the onset of bleeding. When hormone-withdrawal bleeding failed to occur at the end of 10 days, another series of therapy was initiated and the dosage level was increased. Observations included data upon dosage, the initiation of bleeding, the onset of hormone-withdrawal bleeding and upon the duration of this bleeding.

A total of 68 series of cyclic therapy was given, an average of 3.8 series per patient and a range of 1 to 9 series per patient. Hormone-withdrawal bleeding followed 48 of 68 series of therapy. Its onset ranged from 1 to 9 days after the cessation of treatment, the average being 5.9 days. The average duration of bleed-

ing was 4.5 days. No prolonged or excessive bleeding was induced. The daily dosage of sodium estrone sulfate which was associated with withdrawal bleeding ranged from 2.5 to 12.5 mg. and averaged 5.9 mg. These data upon the effective dosage for the induction of bleeding and the time and duration of hormone-withdrawal bleeding are practically the same as those secured with similar oral and cyclic therapy with diethylstilbestrol (5, 6). No correlation between the dosage level and the time of hormone-withdrawal bleeding was established.

Bleeding began just prior to the end of a series of therapy given to 3 patients. When this occurred, treatment was discontinued and resumed five days later.

Bleeding failed to follow 17 series of therapy given to 7 patients. Bleeding was induced subsequently in 5 of these patients when dosage levels were increased. Two patients failed to bleed following sodium estrone sulfate therapy, despite increases in dosage levels. Brief protocols of these two cases are included.

Case 1. A 19-year-old, white, single female with intrinsic adolescent hypoestrogenism, characterized by hypogenitalism and dwarfism (Turner's syndrome), experienced her first uterine bleeding following cyclic and oral therapy with daily doses of 10 mg. of diethylstilbestrol. Seven series of oral and cyclic sodium estrone sulfate therapy were given: two series, 7.5 mg. daily; two series, 10.0 mg. daily; two series, 12.5 mg. daily; and one series, 15.0 mg. daily. No bleeding followed. Genital and mammary development, however, did result.

Case 2. A 22-year-old, colored, single female, who had been amenorrheic since 18 years of age, failed to bleed following a series of oral and cyclic therapy employing daily 1 mg. of diethylstilbestrol but bled when the daily dosage was increased to 2 mg. Three series of oral and cyclic sodium estrone sulfate therapy were given of 2.5, 5.0 and 7.5 mg. daily, respectively. No bleeding followed.

With the exception of the cases of these two patients, all series of therapy which were not followed by bleeding employed daily doses of 5.0 mg. or less of sodium estrone sulfate.

All therapy was tolerated well and no untoward subjective symptomatology ensued. Several of the patients experienced deep brown pigmentation of the areolae, nipples and linea alba—a relatively common observation with diethylstilbestrol therapy.

DISCUSSION

Hormone-withdrawal bleeding, comparable in amount and duration to menstrual flowing, followed oral and cyclic therapy with sodium estrone sulfate in 16 of 18 amenorrheic women. The dosage required to initiate bleeding varied from individual to individual but this apparently was constant for the same individual. Some patients consistently experienced hormone-withdrawal bleeding following series of therapy employing daily 2.5 mg. of sodium estrone sulfate, whereas others required daily doses of 7.5 to 10.0 mg. for the induction of bleeding.

When given orally and cyclically the dosage requirements in milligrams are essentially the same for sodium estrone sulfate and diethylstilbestrol. Likewise the time of onset of hormone-withdrawal bleeding and the duration of bleeding are essentially the same when these two estrogens are employed. Sodium estrone sulfate has the advantage of being tolerated better by patients; diethylstilbestrol has cheapness in its favor.

SUMMARY

Hormone-withdrawal bleeding was induced in 16 of 18 women with functional amenorrhea by oral and cyclic therapy with sodium estrone sulfate wherein daily dosages ranged from 2.5 to 12.5 mg. The average time of hormone-withdrawal bleeding following 20 consecutive days of therapy was 5.9 days and the range was 1 to 9 days. This bleeding was comparable in amount and duration to normal menstruation. The dosage required for hormone-withdrawal bleeding was fairly constant for an individual but varied with different individuals. When assayed by the clinical method of inducing bleeding in functional amenorrhea, sodium estrone sulfate and diethylstilbestrol have essentially the same potency milligram for milligram.

REFERENCES

1. Freed, S. C., W. M. Eisen and J. P. Greenhill: *J. Clin. Endocrinology* 3: 89. 1943.
2. Gray, L. A.: *J. Clin. Endocrinology* 3: 92. 1943.
3. Glass, S. J., and G. Rosenblum: *J. Clin. Endocrinology* 3: 95. 1943.
4. Sevringhaus, E. L., and R. St. John: *J. Clin. Endocrinology* 3: 98. 1943.
5. Palmer, A.: *Am. J. Obst. and Gynec.* 44: 56. 1942.
6. Turner, V. H., C. D. Davis and E. C. Hamblen: Unpublished data.

Oral Therapy With Sodium Estrone Sulfate. II. Induction of Hemostasis and Cycle Regulation in Functional Uterine Hemorrhage[1]

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We have shown in a previous communication that sodium estrone sulfate[2] and diethylstilbestrol, when administered orally and cyclically, compared favorably as regards the dosage in milligrams which is required to induce bleeding in functional amenorrhea (1). The present communication reports results of oral therapy with sodium estrone sulfate for the purpose of inducing hemostasis and cycle regulation in functional uterine hemorrhage. The results of a similar study with diethylstilbestrol have been published and are available for comparative purposes (2).

THERAPEUTIC SCHEDULES

Diagnostic studies of all women selected for therapy established the functional character of the uterine hemorrhages.

For hemostasis, sodium estrone sulfate was given orally in daily doses which varied from 5.0 to 12.5 mg. As a rule, the initial daily dose was 5.0 to 7.5 mg. This was increased to 12.5 mg. daily when bleeding continued. When bleeding ceased, cyclic oral therapy with sodium estrone sulfate was initiated for regulation of the bleeding cycle.

For cycle regulation, sodium estrone sulfate was given orally in daily doses which ranged from 2.5 to 12.5 mg. Therapy was given for 20 consecutive days after hemostasis occurred. There was allowed then a hormone-withdrawal period during which bleeding occurred. Another similar series of therapy was resumed 5 days after the onset of hormone-withdrawal bleeding. When bleeding occurred before a series was completed, therapy was discontinued and resumed 5 days later. One to four series of this therapy were given each patient.

Data on Hemostasis

Fourteen patients were treated. Their ages ranged from 14 to 31 years. The duration of the immediate uterine hemorrhages at the beginning of therapy varied from 7 days to 20 months, the average being 3.6 months. The hemoglobin values of these patients ranged from 6.9 to 14.0 gm.

Prompt hemostasis was secured in 12 of the 14 patients. The time required for hemostasis ranged from 2 to 7 days, averaging 4.1 days. Eventual hemostasis was obtained in another of the 14 patients by increasing the daily dose of sodium estrone sulfate from 7.5 to 12.5 mg. Furthermore, hemostasis was produced twice in one patient. Therefore, hemostasis was produced 14 times in 13 of 14 patients. The one patient, in whom there was failure of hemostasis, received daily doses of 7.5 mg. of sodium estrone sulfate for 12 days and for an additional 8 days, daily doses of 12.5 mg. The relation of dosage to the time required for hemostasis is summarized.

Daily dose, mg.	5.0	7.5	12.5
Average time required for hemostasis, days	5	4.25	3.6
Number of times hemostasis was secured	1	8	5

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[1] Part of the expenses of these studies was defrayed by a grant to one of us (E.C.H.) from the Research Council of Duke University.

[2] Premarin, supplied by Ayerst, McKenna and Harrison, Ltd., Montreal, Canada.

Data on Cycle Regulation

Twenty patients were treated. Their ages ranged from 14 to 31 years. The duration of the periods of prolonged, excessive and/or too-frequent bleeding of these patients ranged from 6 months to 18 years, the average being 5.9 years. Hemostasis had been secured in 13 of the 20 patients by sodium estrone sulfate therapy. It had been secured in the remainder by diethylstilbestrol therapy or curettage. A total of 27 curettages had been done at various times and by various physicians upon these 20 patients because of uterine hemorrhages.

A total of 42 series of cyclic and oral therapy with sodium estrone sulfate was given. The number per patient ranged from 1 to 4, the average being 2.1. Hormone-withdrawal bleeding occurred following cessation of 33 of the 42 series of therapy. The time of appearance of this bleeding ranged from 1 to 19 days, the average being 4.7 days. During 9 series of therapy, bleeding began 1 to 4 days prior to projected completion of the series. No prolonged or excessive bleeding occurred during the period of treatment.

The relationship of dosage to the appearance of hormone-withdrawal bleeding and of bleeding during therapy is summarized.

Daily dose, mg.	2.5 to 3.75	5.0 to 7.5	10 to 12.5
Average latent period for hormone-withdrawal bleeding, days	2.9	5.0	6.8
Number of series of therapy	10	17	6
Average time of onset of bleeding, prior to projected completion of therapy, days	1.8	2.0	1.0
Number of series of therapy	6	2	1

DISCUSSION

Hemostasis was secured promptly by oral sodium estrone sulfate therapy in 14 episodes of uterine hemorrhage of 13 patients. Hemostasis was not obtained during an uterine hemorrhage of one patient. Nine of the 14 instances of hemostasis (64 per cent) were secured with daily doses ranging from 5 to 7.5 mg. This compares favorably with hemostasis obtained with diethylstilbestrol: 60 per cent of instances was secured with daily doses of 6 mg. (2).

Cycle regulation in this group of patients with uterine hemorrhages by oral and cyclic sodium estrone sulfate therapy was even more satisfactory than in the group with functional amenorrhea previously reported (1). The time of occurrence of the hormone-withdrawal bleeding and the required daily oral dosage in mg. of sodium estrone sulfate and diethylstilbestrol are essentially the same (2, 3).

These studies and ones previously reported by us indicate that any statements made that estrone is much less potent when given orally than diethylstilbestrol, one report having estimated it to be one-twenty-fifty as potent (4), do not apply to sodium estrone sulfate. When judged by its ability to induce bleeding in functional amenorrhea, to secure hemostasis in functional uterine hemorrhage and to regulate the cyclicity of bleeding in both of these conditions, sodium estrone sulfate is essentially as potent milligram for milligram as diethylstilbestrol.

All patients tolerated sodium estrone sulfate well; no untoward reactions were encountered.

SUMMARY

The oral administration of sodium estrone sulfate in daily doses of 5.0 to 12.5 mg. produced hemostasis in 13 of 14 women with functional uterine hemorrhage within 2 to 7 days; the average time required for hemostasis was 4.1 days.

Following hemostasis the bleeding cycles of 20 women with functional uterine hemorrhage were regulated satisfactorily by oral and cyclic therapy with 2.5 to 12.5 mg. daily doses of sodium estrone sulfate. Hormone-withdrawal bleeding followed 33 series of this therapy, its average time of occurrence after 20 consecutive days of therapy was 4.3 days. Bleeding occurred 1 to 4 days before projected completion of 9 series of therapy. No excessive or prolonged bleeding occurred during therapy. The dosage in mg. of sodium estrone sulfate and diethylstilbestrol required for these results are essentially the same.

REFERENCES

1. Turner, V. H., C. D. Davis and E. C. Hamblen: *J. Clin. Endocrinology.* 3: 453, 1943.
2. Cuyler, W. K., E. C. Hamblen and C. D. Davis: *J. Clin. Endocrinology* 2: 438. 1942.
3. Palmer, A.: *Am. J. Obst. and Gynec.* 44: 56. 1942.
4. Greenblatt, R. B., R. Torpin and W. R. Brown: *Sou. M. J.* 33: 1276. 1940.

A Contribution to the Treatment of Amenorrhea[1]

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THE TIME is recalled when, in cases of functional amenorrhea of one or two years' duration, the patient was advised that a period of at least 6 months' treatment would be required before results, favorable or conclusively negative, could be obtained. The availability of potent estrogenic preparations subsequent to the isolation and synthesis of the female sex hormones has brought about an appreciable reduction in the length of treatment. Nonetheless, the method of treatment devised by Kaufmann (1, 2), which is commonly employed with slight variations, lasts 25 days and necessitates, according to Zondek (3), a minimum of 13 injections, 8 of the follicular hormone and 5 of progesterone. It was believed that in order to produce uterine bleeding in amenorrhoic women, the estrogenic hormone had to be administered first, to stimulate complete proliferation of the uterine mucosa, and then the secretory phase could be induced by the administration of corpus luteum hormone. Zondek, Rozin and Vesell (4) demonstrated that it is unnecessary to bring about initially a complete proliferation of the uterine mucosa with estrogen in order to produce bleeding with progesterone. In cases of secondary amenorrhea of less than two years' duration, Zondek (3) administered in one injection 12.5 mg. of progesterone plus 1.25 to 2.5 mg. of estradiol benzoate and repeated this dose on two consecutive days. In cases of secondary amenorrhea of more than two years' duration, bleeding could frequently be induced by administering a total dose of 50 mg. of progesterone within a period of 2 to 5 days. Primary amenorrhea and amenorrhea due to castration were treated by the daily administration of 10 mg. of progesterone combined with 0.5 to 1.0 mg. of estradiol benzoate for 5 injections. In all cases, bleeding occurred from 72 to 120 hours after the last injection. Zondek's new method of treatment obviously has several advantages It obviates the use of large doses of estrogens which have an inhibitory effect on the anterior pituitary; it reduces the duration of treatment from 25 days to 2 to 5 days; and, finally, it eliminates a large number of injections and does not accentuate the inferiority complex of the women under treatment.

The apparent superiority of this new method of therapy suggested its employment in the present series consisting of 5 patients with primary amenorrhea, ranging in age from 21 to 40 years of age (table 1), and of 9 patients with secondary amenorrhea of 4 months' to 4 years' duration, ranging in age from 19 to 38 years (table 2). In both groups, constitutional disorders (such as syphilis, tuberculosis and anemia) and local pelvic pathology (such as congenital malformation, degenerative or inflammatory lesions and neoplasms) had been carefully ruled out as etiologic factors of the amenorrhea. The absence of menstruation was pre-eminently due to inherent ovarian deficiency.

While it is fully realized that the acme of therapy would be to produce ovulation, attempts to stimulate the ovaries by administration of gonadotropins have met with only rare success, as most workers in the field agree. Thus, in functional amenorrhea substitutional therapy with estrogens and progestogens is the most practicable method and outweighs in therapeutic value all attempts at stimulating the ovaries to normal function. The conviction has long been held that other than thyroid medication, occasionally successful, the therapy of choice is substitutional.

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[1] This report is concerned with work done in Brooklyn, N. Y., prior to the author's entry into military service.

TABLE 1. INDUCTION OF BLEEDING IN 5 CASES OF PRIMARY AMENORRHEA

Case No.	Age yr.	Wt. lb., Ht. in., and Remarks	Previous Treatment	Present Courses of Treatment[1]							
				1st Mo.	Results[2]	2nd Mo.	Results	3rd Mo.	Results	4th Mo.	Results
1, MK	21	125, 63. Appendectomy 4 yr. ago, uterus and ovaries not examined		5×10 mg. P.		3×1.66 mg. E.B. +3×20 mg. P.	+(6/3)	5×(10 mg. P. +1 mg. E.B.)	+(3/4)		
2, JB	29	175, 60. Obese, short, hypopituitary-thyroid type	Gr. II, b.i.d. of thyroid for 2 mo., Gr. II t.i.d. thyroid for 1 mo. No menses	5×(10 mg. P. +1 mg. E.B.)	+(6/6)	5×(10 mg. P. +0.5 mg. E.B.)	+(2/5)				
3, SS	32	120, 62.	Pituitary and chorionic gonadotropin. No menses	5×100 mg. Preg.		5×(10 mg. P. +1 mg. E.B.)	+(8/3)	5×10 mg. P.		3×(10 mg. P. +1 mg. E.B.) +1×(20 mg. P.+2 mg. E.B.)	+(3/2.5)
4, MB	40	118, 67.		3×(10 mg. P. +1 mg. E.B.) +1×(20 mg. P. +2 mg. E.B.)	+(4/4)	2×(20 mg. P. +2 mg. E.B.) +1×(10 mg. P. +1 mg. E.B.)	+(5/2)	2×(25 mg. P. +2.5 mg. E.B.)	+(3/2)	No therapy	
5, LB	33	121, 62.		3×(10 mg. P. +1 mg. E.B.) +1×(20 mg. P.+2 mg. E.B.)	+(3/3)	No therapy		3×(10 mg. P. +1 mg. E.B.) +1×(20 mg. P. +2 mg. E.B.)	+(4/3)	2×(25 mg. P. +2.5 mg. E.B.)	+(3/4)

[1] *KEY*. E.B., estradiol benzoate; P., progesterone; Preg., pregneninolone.
[2] First figure in brackets under results indicates day of occurrence of bleeding following last injection; second figure indicates duration of bleeding.

TABLE 2. INDUCTION OF BLEEDING IN 9 CASES OF SECONDARY AMENORRHEA

Case No.	Age, yr.	Wt., lb.; Ht., in. and Remarks	Menarche, Type of Bleeding	Duration of Amenorrhea mo.	Previous Treatment	Present Courses of Treatment[1]							
						1st Mo.	Results[2]	2nd Mo.	Results	3rd Mo.	Results	4th Mo.	Results
1 VC	19	112, 68. Tall, thin, single	16.5 yr., irreg., q. 30–40 days	30	None	5×10 mg. P.	+(3/3)	3×10 mg. P.	+(5/2)	2×(12.5 mg. P.+ 2.5 mg. E.B.)	+(2/3)		
2 MD	21	118, 65. Single	13 yr., reg. to 2 yr. ago. irreg. since q. 4–5 months	12	Estrogenic hormone injections, 12 in no. No bleeding. Dosage ?	4×10 mg. P.	+(3/4)	5×100 mg. Preg.	+(6/6)				
3 MF	32	140, 64. Para 1, aet. 7	14 yr., regular to 30 yr. Thought herself pregnant. D & C done (Pregnancy?) No bleeding since	18	Injections (type?) of no avail	5×10 mg. P.	+(4/4)	2×(12.5 mg. P.+ 2.5 mg. E.B.)	+(3/2)	No therapy	+(30 days after last bl./3)		
4 MG	29	132, 63. Married, aborted 4 yr. ago. (Cause?). Gain in wt. of 15 lb. last 2 yr.	16 yr.; regular q. 30–31 days to 3 yr. ago. Irreg. for 1 yr., followed by amenorrhea	18	None	30 mg. P. 1st day, 20 mg. P. 2nd day	+(4/2.5)	No therapy	+(28 days after last bl./2)	No therapy	+(30 days after last bl./3)		
5 SF	21	128, 64. Nulligravida	14 yr.; regular to 7 mo. ago. ("Just stopped")	7	D & C when missed periods. Reason ?	2×(20 mg. P.+1.5 mg. E.B.)	+(4/4)	No therapy		2×(12.5 mg. P+ 2.5 mg. E.B.)	+(3/3)		
6 SJ	38	142, 63. Para 2, aet. 11 and 3 yr.	13 yr.; normal. Irreg. last 4 yr.	42	Hormones and thyroid injections resulting in spotting ("Not like menstruation")	Thyroid gr. I b.i.d. + 2×(100 mg. Preg.+ 2 mg. E.)	+(8/3)	4×(12.5 mg. P.+ 2.5 mg. E.B.)	+(3/2)	No therapy		2×(12.5 mg. P.+ 2.5 mg. E.B.)	+(3/3)
7 AB	27	118, 62. Para 1, aet. 4 yr.	14 yr., normal to birth of child, no menses since (nursed baby 11 months)	48	Various hormones by mouth and injection, dosage unknown; no effect	4×(12.5 mg. P.+1.25 mg. E.B.)	+(3/4)	2×(12.5 mg. P.+ 2.5 mg. E.B.)	+(3/4)	No therapy		No therapy	
8 LMcD	32	136, 63. Single	16 yr.; normal to 4 mo. ago.	4	None	2×(12.5 mg. P.+ 2.5 mg. E.B.)	+(3/3)	No therapy		2×(12.5 mg. P.+ 2.5 mg. E.B.)	+(3/4)		
9 GB	30	112, 65. Thin, pale. Nulligravida	19 yr., q. 3–4 from start	11	Occasional injection; no effect	2×(12.5 mg. P.+ 2.5 mg. E.B.)	+(4/3)	2×(12.5 mg. P.+ 2.5 mg. E.B.)	+(3/4)	No therapy		No therapy[3]	

[1] *KEY*. E., estradiol; E.B., estradiol benzoate; P., progesterone; Preg., pregneninolone.
[2] First figure in brackets under results indicates day of occurrence of bleeding following last injection—second figure indicates duration of bleeding.
[3] No therapy was given in the 5th and 6th months. Patient had periods each time.

In the cases of primary amenorrhea, a total of 5 mg. of estradiol benzoate and 50 mg. of progesterone administered intramuscularly in divided doses, in most instances over a period of 5 days, elicited bleeding in all patients. It was also possible to produce initial bleeding by administering the 5 mg. of estradiol benzoate and 50 mg. of progesterone within only 4 days (*Patient M.B.* and *L.B.*). Subsequent bleedings could be brought about in these two cases by giving the same total dosage within a 3 and even a 2-day period. One patient (*J.B.*), who had responded favorably to the 5-day treatment plan, during the next month responded to a smaller dose of estradiol benzoate, 2.5 mg., which together with 50 mg. of progesterone given in divided doses over 5 days was followed by bleeding which ensued within 2 days. In no case of primary amenorrhea did bleeding take place in subsequent months without therapy. Likewise, progesterone alone, whether given parenterally or orally, was not found to be productive of bleeding. This seems to indicate the necessity of 'priming' the endometrium with estrogenic hormone in cases of primary amenorrhea which, however, may be given either previously to or concurrently with the progesterone.

According to Zondek, patients with secondary amenorrhea, except in the most severe cases, do not require priming with estrogenic hormone; bleeding can be elicited by administration of corpus luteum hormone alone. In three of our patients bleeding ensued after administration of a total of 50 mg. of progesterone. In two instances (*V.C.* and *M.F.*) the dose was given over a 5-day period and in one (*M.G.*), over 2 consecutive days. In one of these (*V.C.*), during the month following the first series of injections, the dose was reduced to 30 mg. of progesterone injected in divided doses on 3 consecutive days and again bleeding was produced. Likewise, a total of 40 mg. of progesterone, 10 mg. each, on 4 consecutive days, was followed by bleeding (*case M.D.*). In the latter a daily oral dose of 100 mg. of pregneninolone on 5 consecutive days during the following month resulted in satisfactory bleeding. In another case (*S.F.*) who was insistent on immediate results, a daily dose of 20 mg. of progesterone in combination with 1.5 mg. of estradiol benzoate, was administered on two consecutive days and resulted in bleeding after 4 days. In the two cases of amenorrhea of longest duration in this series (*S.J.*, 3.5 years, and *A.B.*, 4 years) Zondek's 2-day treatment plan was extended to 4 days by repeating the course of treatment. In one instance only 1.25 mg. of estradiol benzoate in combination with 12.5 mg. of progesterone were used daily in place of 2.5 mg. of estradiol benzoate which, together with 12.5 mg. of progesterone, were employed in the other as a daily dose. This procedure produced bleeding in both patients. Possibly, a total dose of 50 mg. of progesterone alone given on 4 consecutive days would have produced bleeding just as well, but here again the psychic condition of the patients decided against risking a negative result.

The two-day-treatment plan requiring a total of 25 mg. of progesterone and 5 mg. of estradiol benzoate per treatment, was applied in 7 patients, and produced bleeding in each single instance. In two cases, a second course was given with success. The duration of the amenorrhea in this series of 7 cases varied from 4 months to 4 years. However, a positive response to the administration of 50 mg. of progesterone, in two instances in combination with estradiol benzoate, had preceded the two-day-treatment plan in those cases in which the amenorrhea was of several years' standing (*V.C.*, *S.J.* and *A.B.*). This two-day method of treatment inaugurated by Zondek was found to be ideal and the widespread adoption of this simple, short course of treatment will spare to many women the inconvenience of the prolonged therapy of previous days, which is not only time-consuming but also expensive.

Observation of the patients in the months that followed successful treatment was feasible only in 7 of the group of 9 patients, due to external circumstances. In 12 hypothetical cycles, spontaneous menstruation occurred in 5 instances, while in 7 discontinuation of treatment was followed by cessation of uterine bleeding. Thus it seems that in secondary amenorrhea bleeding can be produced almost at will by hormone administration. However, spontaneous, normal menstrual rhythm does not necessarily follow.

Repeated biopsies made in several cases at

or immediately prior to, the onset of flow have showed that the induced bleeding occurred from a proliferative endometrium. It was observed that progesterone, either alone or in combination with estrogen, is able to produce quite copious bleeding from this type of endometrium be it ever so thin. Thus, in cases of amenorrhea there seems to be no relationship between the architecture of the endometrium and its bleeding-inducing propensities, as long as there is proliferation.

SUMMARY AND CONCLUSIONS

A series of 5 patients with primary amenorrhea and of 9 patients with secondary amenorrhea due to intrinsic ovarian deficiency, is presented and the results with hormone therapy described.

In primary amenorrhea, bleeding was produced by the simultaneous administration of a total of 50 mg. of progesterone and 5 mg. of estradiol benzoate over a period of 4 to 5 days. Progesterone alone was ineffective, priming with estrogenic hormone being essential.

In 7 cases of secondary amenorrhea, a total of 25 mg. of progesterone and of 5 mg. of estradiol benzoate, administered in divided doses on two consecutive days resulted in bleeding.

In 3 cases of secondary amenorrhea a dose of 50 mg. of progesterone given either in divided doses over a period of 5 days or for 2 consecutive days, elicited bleeding. Smaller total doses of the luteal hormone alone (30 and 40 mg.) likewise produced bleeding.

In cases in which the amenorrhea has persisted for more than 2 years, a dose of 50 mg. of progesterone seems to be necessary. When immediate favorable results are imperative, the simultaneous administration of estrogenic hormone is advisable. After bleeding has been obtained, either by the combined medication or by larger doses of progesterone alone, the simplified two-day treatment plan can be applied successfully during following months, even in cases in which the amenorrhea has persisted for several years.

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REFERENCES

1. KAUFMANN, C.: *Klin. Wchnschr.* 12: 1557. 1933.
2. KAUFMANN, C.: *J. Obst. and Gyn., Brit. Emp.* 44: 310. 1937.
3. ZONDEK, B.: *J. Am. Med. Assoc.* 118: 705. 1942.
4. ZONDEK, B., S. ROZIN AND M. VESELL: *Am. J. Obst. and Gyn.* 40: 391. 1940.

Influence of Thyroid Activity upon Renal Function

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SOME theoretical considerations led us to wonder whether the renal function and the amount of functioning renal tissue might not owe their relationship to body surface to an association with the basal metabolic rate. That the functional activity of the kidneys should vary with the basal metabolic rate just as do many other physiological processes, is almost without question, for the nitrogen and water metabolism with which renal activity is intimately concerned are both dependent in large measure on the basal metabolism. However, it is the full possible functional capacity of the organ and not the fluctuations in the level of its functional activity with which we are concerned here. In the normal organism, there always seems to be maintained a wide margin of safety between this ordinary level of functional activity and the total function of which an organ or tissue system is capable. In many conditions in which the usual level of functional activity is increased while the basal metabolism remains normal, the functional capacity is likewise increased in a more or less like degree.

For instance, an athlete who goes into training raises not only his ordinary daily cardiac output but also the maximum possible cardiac output. In the same way, it seemed reasonable to suppose that when the degree of renal activity which normally exists is increased by a higher basal metabolism, the functional capacity of the kidneys would similarly increase. Likewise, similar changes in a reverse direction might be expected when the basal metabolism became lowered.

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Renal function as measured by the ratio of urine urea rate to blood urea concentration, as determined under certain standard conditions, is directly related to the size of the kidneys in animals (1, 2, 3) which, in turn, is closely related to the body surface (4, 3). In man, likewise, (5) both kidney weight and renal function bear a more direct relation to body surface than to other measures of body size. Since the basal metabolism bears a remarkably consistent relation to body surface, this suggests a relation of the renal function to the basal metabolism. In fact, this relationship must exist in normal subjects, but there is no way to demonstrate that it is causal. Recourse was therefore had to the study of patients with an abnormal basal metabolism, and without evidence of a renal lesion.

METHODS

Except for series of observations on three patients which are described later, data were obtained from any patient with either hypothyroidism or hyperthyroidism on whom simultaneous or nearly simultaneous observations of the basal metabolism and the renal function could be made. Data on a few normal individuals were also included. If the determinations were not made on the same morning, the basal metabolism was determined both before and after the renal function was measured, and was found not to have changed appreciably.

The basal metabolism was determined at least 12 hours after the last ingestion of food, and soon after awakening the patient in the morning. It was determined indirectly from the oxygen consumption over a 10-minute

period in the usual manner, with a Sanborn, McKesson or other standard machine designed for this purpose. For calculation of the deviation from normal, the basal metabolism was related to body surface in the usual manner. For the calculation of body surface, the observed height and ideal body weight for this height was used (Baldwin and Wood, 6), unless the observed weight was less than the ideal body weight. In this case, the observed weight was used. The same method was followed in calculating the body surface for reference in measuring renal function.

Renal function was measured by the Addis "Urea Ratio" determined under standard conditions (7). Since this ratio is generally expressed as the urine urea excretion rate in mg. per hour divided by the blood urea concentration in mg. per 100 cc., it is essentially the number of 100 cc. portions of blood cleared of urea each hour (7). The test was usually made by having the subject ingest 15 to 30 gm. of urea with two glasses of water at 6:00 A.M. A similar amount of water was taken at 6:30, 7:00, 8:00, 9:00, 10:00 and 11:00 A.M. Urine specimens were collected at 7:00, 8:00, 9:00, 10:00, 11:00 A.M. and 12:00 N. The first three specimens were discarded. Blood specimens for urea determination were drawn at 9:30, 10:30 and 11:30 A.M. A typical result follows:

Hour	*Urine Vol.*	*Urine Urea* mg./hr.	*Blood Urea* mg./100 cc.	*Urea Ratio*
1	540	1830	61.0	30.0
2	680	1752	58.0	30.2
3	610	1602	54.3	29.5
				29.9 Average

Body surface area was obtained from observed height and ideal body weight (observed body weight higher in this case) = 1.76 sq. m. Average normal urea ratio = 27.7 per sq. m. body surface. $29.9/1.76 \times 100/27.7 = 61.3\%$ renal function.

This procedure has been outlined in some detail because there is an increasing tendency to refer to widely different urea 'clearance' tests as if they gave comparable results (see reference to Bartels in discussion).

RESULTS

The data serving as the basis of this report are listed in table 1. The group included 6 normal individuals (B.M.R. −6 to +3), 14 patients with hypothyroidism (B.M.R. −30 to −6), 5 with myxedema (B.M.R. −38 to −29), 3 with slight elevation of basal metabolism (B.M.R. +7 to +15), 2 with toxic adenomas (B.M.R. +34 and +58), and 11 with exophthalmic goiter (B.M.R. +18 to +71).

TABLE 1. CASES IN WHICH ISOLATED OBSERVATIONS OF THE BASAL METABOLIC RATE AND RENAL FUNCTION WERE MADE

Case No.	Sex	Age	Basal Metabolic Rate	Renal Function
		Years	% deviation from normal	% of normal
		Myxedema		
1	F	42	−38	40
2	F	34	−38	48
3	F	48	−33	21
4	F	55	−32	27
7	F	45	−29	25
		Hypothyroidism		
5	M	64	−30	44
6	F	57	−30	51
8	F	31	−27	38
9	M	50	−27	43
10	M	44	−24	40
11	F	41	−21	55
12	F	37	−20	68
13	F	61	−19	51
14	F	49	−15	77
15	F	28	−13	64
16	M	22	−12	82
17	F	18	− 9	107
18	M	54	− 9	92
19	M	63	− 6	84
		Normal		
20	M	35	− 6	95
21	M	27	− 5	86
22	M	25	− 1	99
23	M	23	0	106
24	M	22	+ 1	110
25	M	24	+ 3	96
		Hyperthyroidism		
26	M	33	+ 7	85
27	F	38	+10	94
28	F	47	+15	115
		Exophthalmic goiter		
29	F	42	+18	111
30	M	34	+19	91
31	F	24	+25	88
32	F	51	+29	72
34	F	60	+36	138
35	F	37	+37	110
36	F	29	+41	100
37	F	44	+44	135
39	F	29	+63	73
40	F	38	+65	113
41	F	56	+71	105
		Toxic adenoma		
33	F	35	+34	67
38	M	40	+58	91

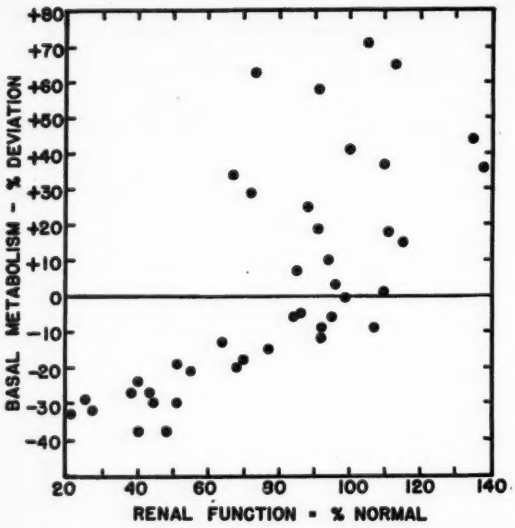

FIG. 1. Data in table 1 presented in graphic form.

There is a definite tendency for the renal function to be low when the basal metabolism is low and vice versa. These data are presented graphically in figure 1. In hypothyroidism, when the basal metabolism is reduced below the normal level, there is a very definite relation between the decrease in the basal metabolism and the renal function. In various types of hyperthyroidism, where the basal metabolism is above normal, there is a tendency for the renal function to be increased, but it is irregular, and the relationship is of a more indefinite nature.

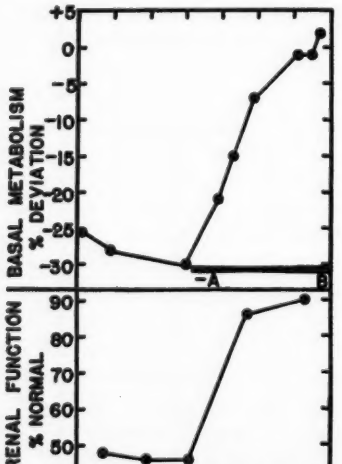

FIG. 2. Observations made on a 69-year-old female with myxedema. She was 58 in. tall and weighed 126 lb. Thyroid medication was stopped for 7 days before the first day of observation. During the period A-B, commencing with the 16th day of observation, she was given 3 grains of U.S.P. desiccated thyroid daily. At no time was there urinary evidence of any renal lesion.

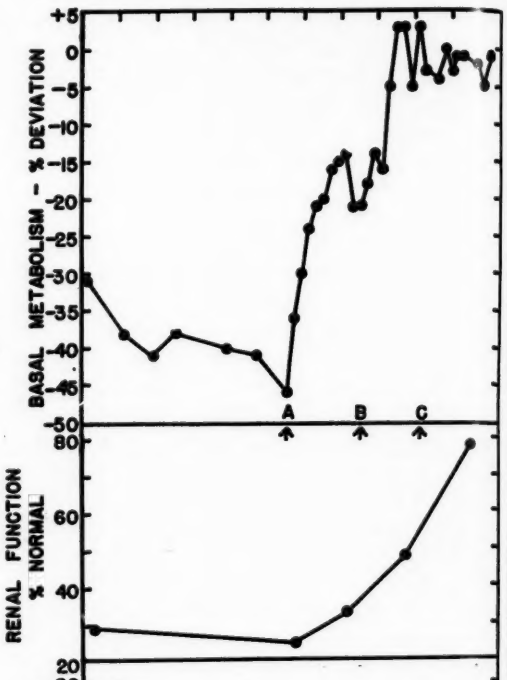

FIG. 3. Observations made on a 26-year-old female with myxedema. She was 66 in. tall and weighed 158 lb. There had been no previous thyroid medication. In spite of the high blood urea concentration at the height of hypothyroid symptoms, the urine protein content was only slightly greater than normal. The urinary sediment did not indicate the presence of a significant renal lesion. Following thyroid therapy, the faintly positive qualitative test for protein in the urine became negative. At A, B and C, 13.5, 10.0 and 2.0 mg. of thyroxin, respectively, were administered intravenously.

In figure 2 and 3 are observations on two cases of myxedema which were observed without and with thyroid therapy over a period of

TABLE 2. OBSERVATIONS ON A 28-YEAR-OLD MALE WITH GRAVES' DISEASE

Day of Observation	Basal Metabolism % of normal	Renal Function % of normal
1	+62	155
4		138
6	+45	
12	+36	138
15	+44	
21	+36	122
22	+38	
23	Ligation of superior thyroid arteries	
26	+13	
28	+14	97
33	+46	117
36	+48	

days. These series of observations lend strong support to the relationship demonstrated by the observations on individual patients which are plotted in figure 1. Although the renal function does not react as rapidly or markedly to thyroid therapy as does the basal metabolism, the dependence of the renal function on the latter is obvious.

Patients with hyperthyroidism are generally so ill by the time they seek medical attention, and then are being prepared for operation, that a series of observations is not possible. In one case, a severe and unusual exopthalmic goiter in a young male, it was possible to repeat the renal function measurements during a period of several weeks (table 2). Less than the usual amount of water was administered in these tests. Lugol's solution, bed rest and a high caloric intake led to some improvement. The renal function, as well as the basal metabolism, declined. Ligation of the superior thyroid arteries was followed by a still further but transient reduction in both values.

DISCUSSION

These are two points for discussion in regard to the data presented here. One concerns the failure of Bartels (8) to find any relation of the renal function to the basal metabolism in patients with hyperthyroidism. A partial explanation for this may be found in the next paragraph, but his conclusions are perhaps chiefly due to the nature of the method used to measure renal function. No details are given, but the method appears not to be possessed of great accuracy and may be unsuitable for measuring functional capacity.

The correlation between the renal function and the basal metabolism when the latter is reduced below normal is essentially what we might have predicted. Why, then, is this relationship not continued in the ranges of basal metabolism above normal? Of course it is, in part, but the relationship is not of the high order found at the low levels. There are many possible explanations for this. The most likely one appears to be related to the qualitative disturbances in physiological functions. In normal individuals, or in patients with hypothyroidism, the renal function test may be carried out without urea ingestion and adequate urine volumes obtained. In the hyperthyroid patients, this is not the case. Even with urea, the usual diuresis frequently does not occur, and many observations had to be discarded because of this. The observations which were used were not, as a rule, as satisfactory as those made at the lower levels of basal metabolism. Hyperactivity of the vasomotor system and the excessive demands of the various tissues and organs for blood may be responsible for the unsatisfactory measurement of renal function in hyperthyroidism.

SUMMARY

Renal function as measured by the Addis "Urea ratio" has been compared with the basal metabolism in patients with hypothyroidism and hyperthyroidism. There is a direct relation between the two. This relationship is more general when the basal metabolism is above than when it is below normal. Possible reasons for this are discussed.

REFERENCES

1. TAYLOR, F. B., D. R. DRURY AND T. ADDIS: *Am. J. Physiol.* 65: 55. 1923.
2. MACKAY, E. M., AND B. O. RAULSTON: *J. Exper. Med.* 53: 109. 1939.
3. MACKAY, E. M.: *Am. J. Physiol.* 100: 402. 1932.
4. MACKAY, L. L., AND E. M. MACKAY: *Am. J. Physiol.* 83: 191. 1927.
5. MACKAY, E. M.: *Arch. Intern. Med.* 50: 590. 1932.
6. FISK, E. L., AND J. R. CRAWFORD: How to Make the Periodic Health Examination. New York, 1927, page 345.
7. ADDIS, T., AND J. OLIVER: The Renal Lesion in Bright's Disease. Pp. 21–37. Paul B. Hoeber, New York, 1931.
8. BARTELS, E. C.: *Trans. Amer. Assn. Study of Goiter.* P. 359. 1938.

Pregnancy Occurring in Cretinism and in Juvenile and Adult Myxedema

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THE IDEA prevails that pregnancy does not occur in women with cretinism or myxedema before thyroid therapy. The reports in the literature, on the other hand, agree that pregnancy can occur but that it is extremely rare. Rolleston (1) was not certain that cretins could become pregnant until after thyroid medication and thought that pregnancy in myxedema without treatment was rare. Goldzieher (2) said that myxedematous women can become pregnant, but that it is exceptional. Herrgott (3) was of the opinion that pregnancy occurred only in the attenuated forms of myxedema. We have been able to find in the literature reports of only 7 cases of adult myxedema and 3 cases of cretinism or juvenile myxedema in which pregnancy occurred before thyroid medication. During the past 12 years we have observed 3 cases of adult myxedema, 2 of juvenile myxedema and 1 of cretinism in which pregnancy occurred after the onset of the disease and before thyroid therapy. These observations lead us to believe that pregnancy occurs more frequently in hypothyroidism than the literature and general opinion would indicate.

FIG. 1. The characteristic objective manifestations of juvenile myxedema (*Case 2*).

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CASE REPORTS

Case 1. A white female, aged 29 years, was admitted to the University Hospitals on July 27, 1931 for a mass in the lower abdomen and vaginal bleeding. The mental deficiency of the poorly nourished individual who appeared approximately 9 years of age, prevented obtaining a coherent and accurate history. The objective manifestations which were typical for cretinism were a mentality of 2 to 3 years, dry, scaly and yellowish skin and, dry and scanty hair. Additional physical findings were a dislocated left hip, an enlarged uterus to that of a 2 months pregnancy, bluish vaginal mucosa, soft and enlarged uterine cervix and colostrum in the breasts. The obstetrical staff was convinced that she had had a complete abortion before admission.

Case 2, M. K. (38-25234). A white female, aged 34 years, was first admitted to the University Hospitals

on July 25, 1938. She had developed normally until 12 years of age. At this time growth ceased and she noted dryness of skin, coarse hair, slow speech, sensitiveness to cold and sluggishness. These symptoms had persisted for 22 years, until admission. Menstruation began at 18 years and recurred regularly each month. At the age of 30 years she became pregnant and delivered a normal full-term infant. The child had grown and developed normally and at the time of admission of the patient he was 4 years of age. She denied any other pregnancy. The patient's parents, 1 sister and 2 brothers were of normal size. One sister also had juvenile myxedema and also had become pregnant before thyroid therapy.

The objective manifestations were typical for juvenile myxedema as seen in figure 1. The additional pertinent physical findings were slow speech, enlarged tongue, small underdeveloped breasts, sparse axillary and pubic hair, umbilical hernia, bilaterally lacerated uterine cervix, basal oxygen consumption, −42 per cent and blood cholesterol of 430 mg. per cent. The usual response to thyroid therapy was obtained.

Case 3. M. H. (*P-2349*). A white female, aged 33 years, was first admitted to the University Hospitals August 6, 1936 for delivery of a full term pregnancy. She had been slow in developing and did not walk until 4 years of age. She was slow mentally and went only to the 4th grade in school. The history was not very coherent or accurate. There was, however, a history of a previous pregnancy, but the child died when about 1 year of age and the details regarding its death were vague.

The objective manifestations were typical for juvenile myxedema and were: lethargic and imbecilic appearance, large head, dry and coarse hair, dry and pale skin, puffy face and eyelids, broad nose, thick lips, large tongue, umbilical hernia, short and broad hands, basal oxygen consumption, −35 per cent and an intelligence quotient of 40.

She delivered a full term normally developed infant of 3950 grams (8.69 lb.) by forceps delivery and the infant died without breathing. She responded in the usual fashion to thyroid medication without much alteration in the mental status.

Case 4. L. T. (*K-547*). A white female, aged 52 years, was admitted to the University Hospitals on July 11, 1934 complaining of an umbilical hernia, and she had typical myxedema. The symptoms of myxedema began insidiously 15 to 20 years previously. The subjective manifestations were: sensitiveness to cold, progressive weakness, dryness of hair and skin, absence of perspiration, loss of axillary hair, slowness of speech and mental processes and puffiness of face. The menses began at 16 years and were regular. They ceased at 51 years. She had had one full term pregnancy and one that terminated at 5 months since the onset of the myxedema.

The objective manifestations were: puffiness of face and eyelids, coarse and dry skin, large tongue, dry and thin hair and basal oxygen consumption, −41 per cent. The usual response was obtained with thyroid medication.

Case 5. L. S. (*J-3632*). A white female, aged 24 years, entered the University Hospitals on April 4, 1934, complaining of anemia, but was found to have myxedema. The menses began at 14 years and were always regular. The subjective manifestations of myxedema began following her first pregnancy 4 years previously and were: sensitiveness to cold, weakness, slowness of mental and physical activity, slow speech, thick tongue and loss of memory. One year after the onset she became pregnant and aborted two months later. Approximately one year later she again became pregnant and delivered a full-term normal infant. The myxedema symptoms increased in severity until admission.

The objective manifestations were apathy, pallor, dry and rough skin, puffiness of face, dry and brittle hair, thick tongue, husky voice, atrophic breasts, scant axillary and pubic hair, basal oxygen consumption, −42 per cent and blood cholesterol 274 mg. per cent. She responded in the usual fashion to thyroid medication.

Case 6. A. M. (*40-1855*). A white female, aged 41 years, entered the University Hospitals on November 19, 1936, complaining of weakness, intolerance to cold and ease of fatigability of 6 years' duration. The symptoms of myxedema became aggravated during pregnancy 2 years before admission. The additional subjective manifestations were clumsiness, puffiness of face, slowed function mentally and physically, and parasthesia. The objective manifestations were coarse and dry skin and hair, large tongue, slow speech, husky voice, basal oxygen consumption, −32 per cent and blood cholesterol 384 mg. per cent. The usual response to thyroid therapy was obtained.

DISCUSSION

We recognize that only one of our cases (*Case 3*) was observed during the pregnancy and that there may be some question regarding the co-existence of pregnancy and cretinism or myxedema in the other cases. All members of the obstetrical staff were convinced that *Case 1* had been pregnant and that she was a typical cretin. The patient in *Case 2* was a typical juvenile myxedema who had not received thyroid therapy previously and who had been pregnant. In *Cases 4, 5* and *6* the pregnancy or pregnancies had occurred after the onset of the myxedema symptoms. Those familiar with myxedema recognize that these patients frequently go for years after the onset of their malady before it is diagnosed and treated. We are convinced that in all three of these cases

the myxedema antedated the pregnancy by months to years.

That there is a relationship between the thyroid and the ovaries has abundant clinical observations to substantiate it. The nature of this relationship is not known. Very few positive results have been obtained from animal experimentations. In the clinic, on the other hand, thyroid hyperplasia is observed at puberty, during menstruation, pregnancy and lactation, and thyroid therapy is definitely established as beneficial in certain cases of menstrual disorders, sterility and habitual abortion. Also a decrease in libido is common in cases of hyperthyroidism and hypothyroidism. Some of these relationships may be through the pituitary gland and others may be direct. If there is a direct relationship between the two glands which causes sterility, with mild hypothyroidism one would anticipate that patients exhibiting complete suppression of thyroid secretion as found in myxedema and cretinism would be universally sterile.

There are probably many reasons why pregnancy does not occur more frequently in myxedema and cretinism or why they are not recognized during pregnancy. First, there are relatively few cretin or juvenile myxedema patients reaching child-bearing age without treatment. Second, the underdevelopment of the genitalia which is frequently associated with cretinism and juvenile myxedema precludes the possibility of pregnancy. Third, many of the patients with adult myxedema have passed the child-bearing age. Fourth, undoubtedly the myxedema is overlooked in some cases coexisting with pregnancy. Fifth, some cases of cretinism and myxedema are secondary to pituitary deficiency which also results in sterility.

These observations show that hyposecretion of the thyroid gland does not invariably produce sterility and indicate that the relationship between the thyroid and the ovary is probably an indirect one. Although not the chief reason, an important one, for the few cases of coexisting myxedema and pregnancy reported is the failure to recognize myxedema in many cases of pregnancy. This is amply illustrated by *Cases 4*, *5* and *6* of our series.

TABLE 1. REPORTED CASES OF PREGNANCY OCCURRING IN CRETINISM AND IN JUVENILE AND ADULT MYXEDEMA

Author	Disease	Year
Townsend	Cretinism	1897
Herrgott	Cretinism	1902
MacIlwaine	Myxedema	1902
Howard	Myxedema	1907
Howard	Myxedema	1907
Audebert and Claverie	Myxedema	1921
Plummer	Myxedema	1922
Merguet	Cretinism	1922
Fruhinsholz	Myxedema	1925
Kirk	Myxedema	*
Parkin and Greene	Myxedema	
Parkin and Greene	Myxedema	
Parkin and Greene	Myxedema	
Parkin and Greene	Juvenile myxedema	
Parkin and Greene	Juvenile myxedema	
Parkin and Greene	Cretinism	

* Rolleston cites Kirk, The Endocrine Organs in Health and Disease 1936, Oxford Univ. Press, p. 187.

SUMMARY

One case of cretinism, 2 of juvenile and 3 of adult myxedema are reported in which pregnancy occurred after the onset of the disease and before thyroid therapy was instituted. A review of the literature reveals that only 10 such cases have been reported previously. The relationship between the thyroid and ovarian glands and the causes for the rarity of reports of pregnancy co-existing with hypofunction of the thyroid gland are discussed.

REFERENCES

1. ROLLESTON, H. D.: The Endocrine Organs in Health and Disease. Oxford University Press, pp. 170 and 187. 1936.
2. GOLDZIEHER, M. A.: The Endocrine Glands. D. Appleton-Century Co. p. 123. 1939.
3. HERRGOTT, A.: Myxoedeme, parturition et eclampsie. *Annales de Gynecologie* 58: 1. 1902.
4. TOWNSEND, C. W.: A pregnant cretin. *Arch. Ped.* 14: 20. 1897.
5. MACILWAINE, S. W.: Myxedema in mother and child. *Brit. Med. J.* 1: 1261. 1902.
6. HOWARD, C. P.: Myxedema: A study. *J. Am. Med. Assoc.* 48: 1226; 1325; 1403. 1907.
7. AUDEBERT AND CLAVERIE: Grossesse chez une myxoedemateuse. *Bull. Soc. d'obst. et de gynec de Par.* 10: 79. 1921.
8. PLUMMER, S. W.: Pregnancy occurring in a case of myxedema. *University of Durham College of Med. Gazette* 22: 58. 1921–1922.
9. MERGUET: Schwangerschaft bei Sporadischem Kretinismus. Abst. *Klin. Wchnschr.* 1: 971. 1922.
10. FRUHINSHOLZ, A.: Grossesse et myxoedeme. *Bull. Soc. d'obst et de gynec de Paree.* 14: 419. 1925.

Insulin Lipohypertrophy

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THE FOLLOWING study was instigated by the observation of two diabetic patients with extensive areas of lipohypertrophy at the site of insulin application in one of whom lipomata were present also elsewhere on the body.

Tumefactions after insulin injections may occur as granuloma or as fatty hypertrophy. The granulomata are nonspecific inflammatory reactions against chronic traumatization. They are not a specific insulin effect, may develop after any kind of periodic subcutaneous treatment, and have been observed, for instance, after morphine, digitalis and liver extract injections. They are found more frequently after insulin only because no other substance is given so regularly and over so prolonged periods of time. Granuloma consist of small solid lumps which seldom exceed the size of a walnut; they are fixed to the overlying skin and are painless. Histologically they show connective tissue granulation and small round cell infiltration. Insulin granulomata are frequent and may be found in patients of both sexes and all ages, especially in cases in which the injections are given repeatedly into the same spot, and in which no proper care is taken for asepsis.

Instances of fatty hypertrophy after insulin are rare and occur predominantly in juvenile patients (1–4). They consist of large subcutaneous masses over which the skin is easily movable. They are painless, like the granulomata, but their consistency is soft. They can be differentiated from localized edema by the absence of pitting. They may be lobulated and sharply defined from the surrounding tissue or may diffuse gradually without demarcation. Occasionally they are surrounded by areas of lipatrophy. The skin and subcutaneous tissue is not indurated and shows neither scar formation nor signs of allergic or inflammatory reaction. These tumefactions usually extend far beyond the site of injection and affect the whole surface of the thighs, the upper arms, the buttocks or wherever insulin is injected. No other than insulin treatment has been found to cause lipohypertrophy. Since insulin also may cause lipatrophy and since both lesions may occur together, they have been referred to frequently as insulin lipodystrophy.

Only 18 case reports of insulin lipohypertrophy could be found in the literature;[1] they are summarized in table 1. The clinical picture in all of these cases is so similar that there can be little doubt that they represent identical lesions, although biopsies or autopsies were performed in 4 cases only (cases 1, 5, 11, 16). The histological examination in these instances revealed the typical picture of hypertrophic fat tissue with no or only slight signs of inflammation.

Table 1 demonstrates very well the predominance of juvenile cases. Sixteen patients were younger than 20 years and among these 8 were younger than 10 years. The sexes were equally represented, 9 patients being females and 8 males (in one instance the sex was not stated). In their recent paper on insulin lipatrophy, Marble and Smith (16) reported a similar frequency of juvenile cases, but a higher incidence among females than among males. The duration of insulin treatment or of diabetes does not bear a significant relation to the development of lipohypertrophy. In some instances lesions have been observed as early

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[1] The photograph of another, apparently also a juvenile case with typical lesions on both thighs, is reproduced in Duncan's Diseases of Metabolism (W. B. Saunders, Philadelphia, 1942) on page 785, but no history is given.

TABLE 1. SUMMARY OF 18 CASES WITH INSULIN LIPOHYPERTROPHY REPORTED IN THE LITERATURE

Case No.	Author Ref. No.	Age yr.	Sex	Duration of Diabetes yr.	Duration of Treatment yr.	Site of Lipoma	Remarks
1	Eeg-Olofson (5)	16	F	?	1	both thighs	biopsy
2	Gellerstedt (6)	3.5	F	1.5	1.5	outer surface both tighs	disappeared after injection site changed
3	Gellerstedt (6)	5.5	F	2.5	2	both thighs	disappeared after injection site changed
4	Gellerstedt (6)	9	M	5	3.5	both thighs	disappeared after injection site changed
5	Gellerstedt (6)	16	F	8.5	5.5	both arms right thigh	autopsy
6	Rowe & Garrison (7)	8	M	6.5	5	both thighs	decreased after injection site changed
7	Rowe & Garrison (7)	19	F	7	5	both upper arms	
8	Rowe & Garrison (7)	12	F	?	5	both arms	disappeared after injection site changed
9	Rowe & Garrison (7)	50	F	?	1	thigh	
10	Freise (8)	4.5	?	1.5	1	anterior surface both thighs	
11	Priesel (9)	8	M	4	2	anterior surface both thighs	autopsy
12	Priesel (9)	10	M	?	?	both upper arms both buttocks	
13	Adlersberg (10)	20	F	6	?	both upper arms both thighs	no decrease after injection site changed
14	Rosenberg & Berliner (11)	8	M	?	2.5	both buttocks both thighs	
15	Stepp (12)	adult	F	?	?	both thighs	
16	Bader (13)	13.5	M	4	3	both biceps, buttocks and thighs	biopsy
17	Hadorn (14)	9	M	6	2	outer surface both thighs	
18	Nobécourt and Ducas (15)	15	M	6	5	both thighs	decrease after injection site changed

as one year after the beginning of treatment (cases 1, 3, 4) and 1.5 years after the diabetes had been diagnosed (cases 1, 9, 10). The type of insulin does not seem to be significant since some patients used unmodified insulin, others protamine zinc insulin. Several authors (6, 7, 15) observed a decrease or even disappearance of the lipoma when insulin was discontinued or the site of application was changed; others did not (10).

The association of insulin lipatrophy and insulin lipohypertrophy makes it likely that both conditions are caused by a similar mechanism. This mechanism, however, is unknown. Nonspecific inflammatory reactions (11, 17, 18) and specific effects of insulin (19, 20) have been mentioned but have been disproved by the histological findings and the fact that it has not been possible to produce insulin lipodystrophies in normal animals (21). That a predisposition may be necessary for the development of insulin lipodystrophies is suggested by the low clinical incidence (4, 15, 22). The relative frequency in juvenile cases may also be based on such predisposition, since spontaneous lipodystrophies show a similar age distribution (23). Marble and Smith believe that the predisposing factor in lipatrophy is a peculiar susceptibility of the lipase present in the fatty tissue (16).

CASE REPORTS

The histories of both of our patients are typical illustrations of insulin lipohypertrophy. Both were juvenile diabetics. *Patient 1., C.S.*, (290 484), a female, was 20 years old when she came under our observation; she had been diabetic since the age of 3 and had received insulin since the age of 5. When seen by us she had large tumefactions on both thighs (fig. 1) and on the left upper arm; the right upper arm had never been used for injections. There was no accompanying lipatrophy; the scar on the outer surface of the left thigh, which is visible in the picture, is the result of vaccination. The date at which the lipomata were first noted could not be determined, but a photograph showed that the lesion on the left upper arm was already present at the age of 8, 3 years after institution of insulin treatment. The patient was obese and came from an obese family. There was no hereditary tend-

ency to allergic reaction. The patient's insulin requirement had increased gradually and the diabetes was difficult to control. At the time of observation the insulin dosage was 60 units of protamine zinc insulin plus 34 units of unmodified insulin; the diet consisted of 150 gm. of carbohydrates, 70 gm. of protein and 80 gm. of fat. The patient preferred to make the injections into the lipomatous tissue, fearing that a change of site of the injection might give rise to new tumefactions. She was not aware whether occasional severe insulin reactions which she reported occurred when she had injected the insulin into normal tissue.

Patient 2., R.B., (298 563), was an 18-year-old boy who had been diabetic since the age of 8 and had begun insulin treatment one year later. The swelling on his upper arms, which was not accompanied by atrophy (fig. 2) was noticed as early as the age of 10. He had continued to inject the insulin into this area because he had found it least painful there. This boy, too, was obese and came from an obese family. His insulin requirement was increasing steadily, but he did not follow any dietary regime. At the time of observation he gave himself injections of unmodified insulin three times daily (40—20—20), but the urine was never sugar-free. There was no history of allergy and no sign of inflammatory reaction in the area of the lipomata. An interesting finding in this patient was the presence of two lipomata in the abdominal wall, near the umbilicus, each of the size of a plum. The patient did not know when these had developed but he was absolutely certain that he had never injected insulin into this area.

The simultaneous occurrence of lipomata at the site and distant from the site of insulin application has not been observed in any of the reported 18 cases, however, lipatrophies have been found not infrequently both at the site of insulin application and distant from it (2, 22, 25, 26, 27). Since the distant lesions probably represent spontaneous or idiopathic lipodystrophies, the development of which is believed to be based on predisposition (13, 24), these observations seem to confirm that a predisposition for lipodystrophy is an inherent factor for the development of insulin lipodystrophy.

FIG. 1. *Patient 1, C.S.* (290484); insulin lipohypertrophy on both thighs.
Fig. 2. *Patient 2, R.B.* (298563); insulin lipohypertrophy on both upper arms.

SPECIAL EXAMINATIONS

Biopsies were taken from the tumefactions in both cases. They showed identical pictures (fig. 3 and 4). The outstanding features were the hypertrophy of the subcutaneous fat cells and the absence of marked inflammatory signs. The fat cells were large and well filled and numerous lipoblasts were present, a picture which is commonly seen in lipomatosis. Only occasionally a small round-cell accumulation could be seen, mostly around the vessel walls, but there was practically no connective tissue infiltration and no eosinophil cells were present. This gives evidence again that the insulin lipohypertrophy in contradistinction to the insulin granuloma does not represent an inflammatory reaction.

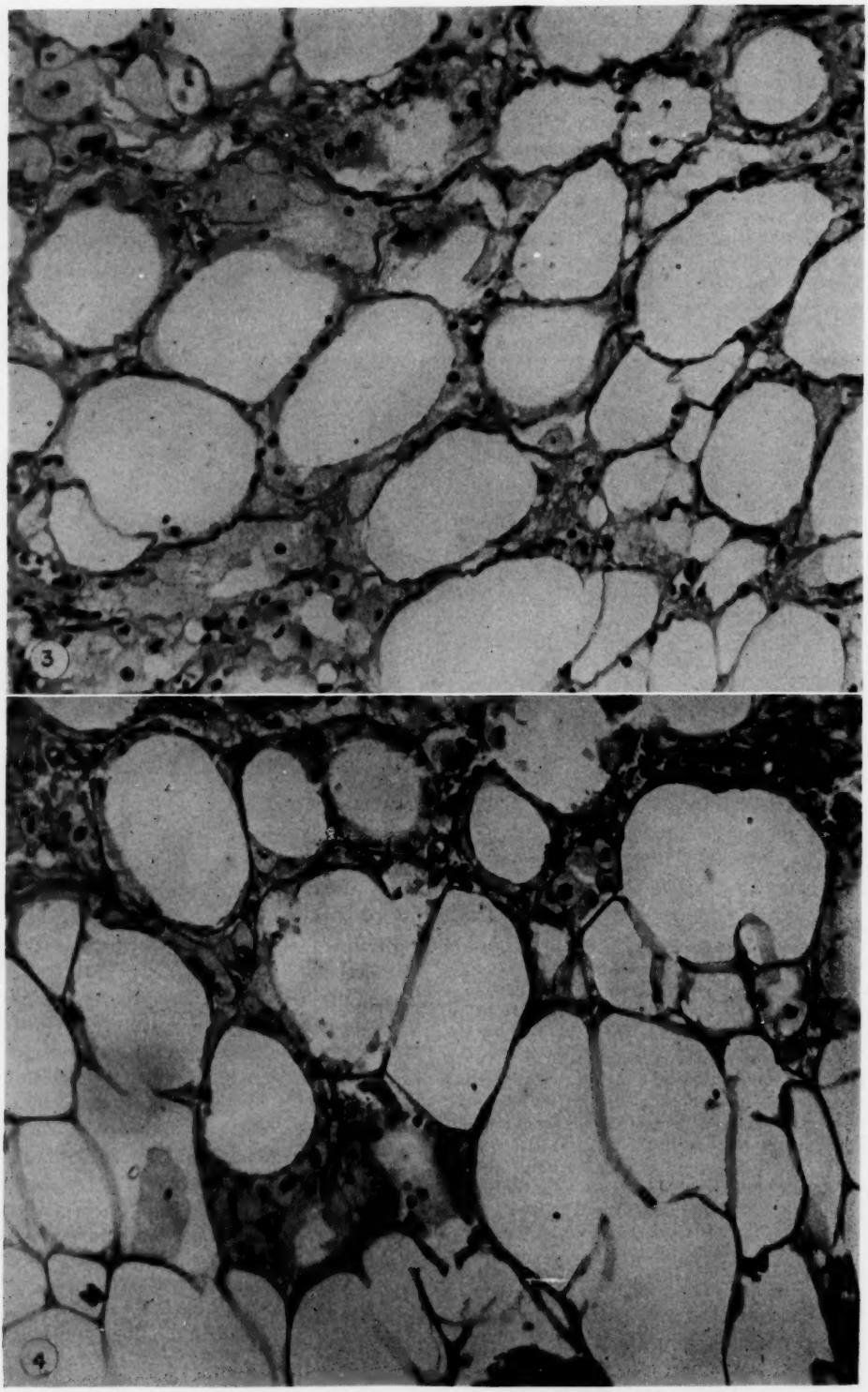

FIG. 3, 4. Biopsies from insulin lipomata in *patients 1* and *2*, respectively. Magnification 1:120. Well filled fat cells, numerous lipoblasts, very few round cells and no increase of connective tissue.

Insulin sensitivity tests were performed in both patients because of the instability of the diabetes. Under fasting conditions and under the condition of withholding the usual morning's insulin dose, 10 units of a solution of insulin zinc crystals was given subcutaneously into the lipomatous area and the blood sugar curve was determined with estimations at fasting and 60, 120, and 180 minutes after insulin injection. On a second occasion the same procedure was repeated with the insulin injected into normal tissue. Figure 5 shows the results as the percentage fall of blood sugar. The curves for *patient 1* are the averges of two test series which were almost identical. There was a characteristic difference of insulin-hypoglycemia depending on the site of injection in both patients. Insulin given into the lipomatous area lowered the fasting blood sugar in *patient 1* by 50 percent and in *patient 2* by 25 percent, whereas the same doses given into normal tissue caused a blood-sugar fall of 82 and 70 percent, respectively. This difference in insulin sensitivity was demonstrated also clinically and accidentally when *patient 1* experienced a severe insulin reaction from half of the usual dosage when it was injected into the abdominal wall instead of the lipomatous area. The cause of this marked difference is probably a delayed absorption from the hypertrophic fat tissue. This became evident from the following experiment.

Intradermal tests with insulin did not produce allergic reactions, but it was noticed that the wheals disappeared much more slowly from the lipomatous area than from normal skin. Control tests with normal saline solution showed the same delay of absorption. Whereas a wheal from 0.1 cc. of saline solution disappeared from the normal skin within 10 minutes, it was still noticeable over the lipomatous area after 45 minutes.

An attempt to produce experimentally insulin lipomata was unsuccessful.[2] The reaction of the subcutaneous inguinal fat bodies of white mice to injections of insulin was studied. Young animals were chosen because of the relative frequency of insulin lipodystrophy among juvenile patients. The animals, from the same stock, were of approximately the same age and the same weight (20 gm.). An insulin solution was prepared which contained

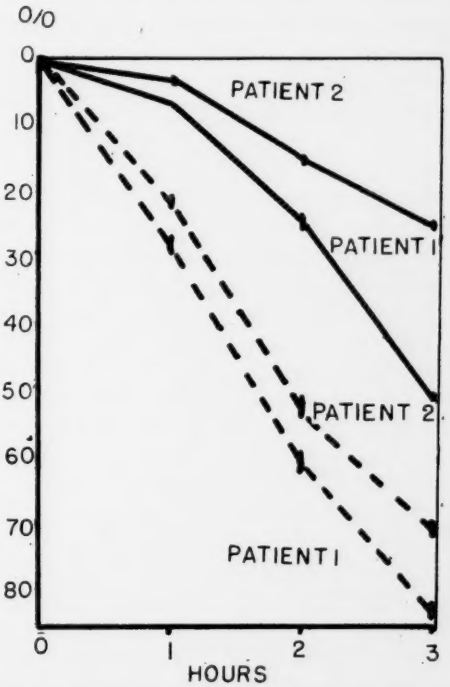

FIG. 5. Comparative curves of the percentage fall of the fasting blood sugar in *patient 1* and *2* after subcutaneous injection of 10 units of a solution of insulin zinc crystals into *a*) the lipomatous area (*solid lines*), and *b*) a normal area (*broken lines*).

2 units in 10 cc. of saline solution. Of this solution, 0.05 cc. or 0.01 unit of insulin could be injected subcutaneously without causing fatal hypoglycemia. One series of 10 animals received daily injections of this amount into one of the inguinal fat bodies. A second series was injected with normal saline solution only. The fat bodies injected with saline and the untreated fat bodies of the insulin-injected group were used as controls. Animals of each series were killed in 5-day intervals and the fat bodies were compared and examined histologically. The last specimens were taken after 40 days of treatment. No significant differences were noted between the fat bodies of the insulin-treated and the control animals. Neither the development of lipohy-

[2] These experiments were made in cooperation with Dr. Friedrich Wassermann, Dept. of Anatomy, University of Chicago, to whom I am indebted for advice and assistance.

pertrophy nor lipatrophy was seen at the site of insulin injections. Macroscopically and microscopically, the size and structure of the fat bodies were identical in all 3 groups. The fat bodies of both the insulin and the saline-treated animals showed signs of mild inflammatory reactions. This result shows again that chronic insulin injection is not sufficient to produce lipodystrophies.

SUMMARY

The literature on insulin lipohypertrophy is summarized and two new cases are reported. Both patients were juvenile diabetics, one of whom also showed lipomata elsewhere on his body. Biopsies proved that the insulin lipohypertrophy is not an inflammatory reaction. When insulin was injected into the lipomatous area, the hypoglycemic response was less severe than when insulin was given into a normal area. This difference is probably due to delayed absorption from the lipomatous area. An attempt to produce insulin lipohypertrophies in white mice was unsuccessful. It is concluded that insulin lipodystrophy occurs in predisposed individuals only.

REFERENCES

1. Priesel, R., and R. Wagner: Die Insulin Lipodystrophie bei Kindern. *Klin. Wochnschr.* 9: 1548. 1930.
2. Beckert, W.: Lipodystrophien and Lipohyperplasien nach Insulin Injektionen. *München med. Wchnschr.* 88: 336. 1941.
3. Alpert, B., and E. A. Ferguson: Local lipoid atrophy and lipoid dystrophy. *Endocrinology* 24: 741.1939.
4. Depisch, F.: Zur Frage der lokalen Lipodystrophie bei Dauer Insulin Behandlung. *Wien. med. Wchnschr.* 80: 168. 1930.
5. Eeg-Olofson, S.: Local changes in the subcutaneous tissue following injections of insulin. *Acta med. Scandinav.* 73: 89. 1930.
6. Gellerstedt, N.: Zirkumskripte Hyperplasie des subkutanen Fettgewebes als lokale Folge von Insulin Injectionen. *Endokrinologie* 10: 412. 1932.
7. Rowe, H., and A. H. Garrison: Lipodystrophy, atrophy and tumefaction of subcutaneous tissue due to insulin injections. *J. Am. Med. Assoc.* 99: 16. 1932.
8. Freise, H.: Case presentation. Kinderärzt. Praxis 3: 382. 1932.
9. Priesel, R.: Lokale Lipomatose nach Insulin Injektionen. *Arch. f. Kinderheilkde* 106: 1. 1935.
10. Adlersberg, D.: Ueber lokale Fettgewebshyperplasie nach Insulin Injektionen. *Med. Klin.* 31: 779. 1935.
11. Rosenberg, M., and F. Berliner: Ueber traumatischen Fettschwund. *Wiener klin. Wochschr.* 49: 1253. 1936.
12. Stepp, W.: Therapy of diabetes mellitus. *München med. Wochnschr.* 82: 1307. 1935.
13. Bader, G. B.: Lipomatosis in areas into which insulin has been injected. *Am. J. of Dis. Child.* 53: 255. 1937.
14. Hadorn, W.: Insulin lipomatosis. *Schweiz. med. Wochnschr.* 18: 516. 1937.
15. Nobécourt, P., and P. Ducas: Lipomatous and atrophic lipodystrophy after repeated insulin injections in diabetic children. *Arch. de méd, d, enf.* 42: 193. 1939.
16. Marble, A., and R. Smith: Atrophy of subcutaneous fat following injections of insulin. *Proc. Am. Diabetes Assoc.* 2: 173. 1942.
17. Avery, H.: Insulin fat atrophy, a traumatic atrophic panniculitis. *Brit. M. J.* 1: 597. 1929.
18. Mentzer, S. H., and E. S. Du Bray: Fatty atrophy from injections of insulin. *California West. Med.* 26: 212. 1927.
19. Carmichael, E., and G. Graham: Local fat atrophy following insulin injections. *Lancet* 214: 601. 1928.
20. Rabinowitch, T. M.: Atrophy of subcutaneous fat following insulin injections. *Canad. M. A. J.* 18: 560. 1928.
21. Reed, L. L., W. E. Anderson and L. B. Mendell: Lipodystrophy from insulin injections. *J. Am. Med. Assoc.* 95: 395. 1930.
22. Rathéry, F., and T. Sigwald: Lipodystrophie localisée insulinique. *Bull. Soc. med. hop. Paris* 54: 951. 1930.
23. Adair, F. E., S. T. Pack and T. H. Farrior: Lipomas. *Am. J. Cancer* 16: 1104. 1932.
24. Ewing, J.: Neoplastic Diseases, fourth edition. W. B. Saunders Company, Philadelphia and London, 1942.
25. Stransky, E.: Lipodystrophie um die und fernab von den Injektionsstellen nach Insulinbehandlung bei Diabetes mellitus. *Wien. med. Wochnschr.* 80: 133. 1930.
26. Boller, R.: Behandlung der Insulin-lipodystrophie. *Klin. Wochnschr.* 9: 2433. 1930.
27. Bertram, F., and H. E. Never: Ueber Insulinlipodystrophien. *Med. Welt* 13: 150. 1939.

Endometrial Biopsy

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THE modern study of the endometrium can rightly be said to date from Recamier's introduction of the curette. Immediately following was an era which witnessed the development of cellular pathology and shed great light on the organic diseases affecting the endometrium. Little progress was made in interpreting functional changes until Hitschmann and Adler's classic paper appeared in 1908. The rapid advances of the last two decades have made possible an experimental approach and this combined with a more enlightened understanding of various clinical phenomena has greatly broadened the scope of knowledge. In general, it may be said that the endometrium reflects the activity of the ovaries.

In recent papers (1–4) we have presented evidence indicating that functional menstrual disorders result from ovarian failure. This may be primary, due to inherent ovarian disease, or secondary, due to extra-ovarian causes such as pituitary, thyroid or other endocrine disease and various types of constitutional disease. The approximate degree of ovarian involvement is indicated by the endometrium.

In studies leading up to the formulation of this concept of ovarian failure, it was desirable to obtain tissue from the same individual at frequent intervals. This led to the development of a method of obtaining bits of endometrium through a suction cannula (5). Later a suction curette and a punch were devised. These methods have been widely used and various modifications have been described from time to time (6–12). By common consent these procedures have come to be known as endometrial biopsy. The purpose of this paper is to evaluate the usefulness of the method. This is dependent upon *a*) the safety of the method and its advantages and limitations as compared with other methods of obtaining endometrial tissue, *b*) the information desired and the extent to which it is obtainable from the biopsy specimen and *c*) correct interpretation of the findings. These, then, are the subjects to be considered.

With regard to the safety of the method, two series of 1500 specimens have been obtained without disaster (7, 13). In our hands, perforation of the uterus and pelvic inflammation have occurred but these complications are extremely rare. From this it may be said that the method is safe provided any reasonable selection of cases is made and undue force in passing the instrument is avoided.

The chief objections to the technic have been summarized by Israel and Mazer (14) in a statement condemning suction biopsy as inadequate for diagnosis due to *a*) the small amount of tissue secured, *b*) the variability of the endometrium and *c*) the inadequacy of the method in the diagnosis of malignancy. These objections are in part offset by the fact that tissue is taken from two or more areas. Nevertheless, the points made by Israel and Mazer are well taken, for these points must be considered in interpreting the biopsy specimen. However, the real measure of the usefulness of the technic is the information that it does afford, not what it may fail to reveal.

The chief advantage of the method, therefore, is that it affords a means of obtaining valuable and often essential information which is not obtainable otherwise. The endometrial

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biopsy technic can be used in cases in which hysterectomy or curettage is not indicated. It can be repeated at relatively frequent intervals. There is no evidence that the procedure has any important effect on the cycle. Finally, the technic has the advantages that it is an office procedure and the specimen can be fixed immediately.

The usefulness of the endometrial biopsy technic for a specific purpose is dependent upon the extent to which the desired information is obtainable by other means and the extent to which the essential criteria are distributed throughout the endometrium. A biopsy specimen is obviously more suitable for diagnosis, which depends upon the recognition of known criteria, than for the study of endometrial structure. No study of the latter type should be limited to biopsy material. However, the method can be used to supplement operative material or to obtain leads for further investigation (15, 16).

In the diagnosis of cancer of the fundus of the uterus the endometrial biopsy technic offers certain advantages. The procedure does not open up blood and lymph channels for spreading of the growth as curettage does. We have observed malignant endometrial emboli in the vessels of the uterine wall after the latter procedure. The possibility of a localized lesion must, of course, be taken into consideration. Curettage should be performed if the biopsy findings are negative. A positive diagnosis of cancer of the uterus can be made from a biopsy specimen in 75 per cent of the cases. Therefore, by correct use of the endometrial biopsy technic, the risk of cancer spread can be greatly minimized without impairing the accuracy of the diagnosis. The evidence of carcinoma in menometrorrhagia is 3.5 per cent according to Israel and Mazer (14), 2.8% according to Douglas (17).

The value and correct use of the endometrial biopsy technic in the diagnosis of other specific pathologic conditions has been discussed by Lörincz and Davis (18) and Mishell (19). The procedure was designed originally and has been used most extensively for obtaining information concerning ovarian function (3, 20–35, 41–43, 47) and particularly for the diagnosis of ovarian failure. Its usefulness for these purposes is dependent first upon the value of the endometrium as an indicator of ovarian function and second upon the extent to which the significant information is obtainable from a biopsy specimen of endometrium.

The best evidence of the value of the endometrial biopsy technic is the great advance in knowledge of ovarian function in the human female that has occurred since the method was introduced. Workers who have used the technic in studying normal and abnormal ovarian function have reported findings which are in general agreement with those of investigators who have made similar studies on material obtained by other means (24–44). This indicates that the accumulated evidence from studies of endometrial biopsy specimens is reliable, as does also the fact that gynecologists who have reported extensive experience with the method have indicated that they consider it a valuable diagnostic procedure (23–34). Campbell, Lendrum and Sevringhaus (24) were among the first to adopt the technic and to point out its value in endocrine diagnosis. Hamblen (32–34) has used the method extensively and found it satisfactory for clinical purposes. Meigs (7) stated, "We have rarely found that these two pieces of tissue vary microscopically and do not believe it is necessary to strip the endometrium with the idea that many different types of endometrium may be found." Our experience has been the same and we have found the method very helpful in many cases.

Critics of the technic of endometrial biopsy have laid great stress on the fact that there is more or less variation in the histologic picture throughout the uterus, as Barthelmez (45) has so beautifully demonstrated. This must be taken into consideration in interpreting the endometrial biopsy specimen, especially in cases of ovarian failure. To determine whether or not this limits the usefulness of the boipsy technic, the nature of the variations that occur and the extent to which significant variaitons are distributed throughout the endometrium must be considered.

The variations described by Barthelmez (45) were structural variations within the limits of the characteristic reaction, not variations in the type of reaction. In the so-called mixed

type of endometrium, the variations in reaction tend to be scattered throughout the endometrium. However, patchy distribution has been observed in some cases of abnormal menstruation and an occasional case in which a variation in the type of reaction was limited to a segregated area has been reported (46, 47).

Confirmation of the above evidence concerning the nature and distribution of variations in endometrial structure and direct evidence for what the biopsy specimen does and does not reveal concerning the state of the endometrium as a whole was obtained recently in our laboratory (48). An endometrial biopsy was made immediately preceding hysterectomy or curettage and the tissue obtained by biopsy was compared with that obtained by operation from the same patient. In the case of hysterectomy, endometrial specimens from different areas of the uterus were compared. The pertinent findings may be summarized as follows.

1. In each of the 56 cases studied, the type of endometrial reaction and the stage of development of the reaction was the same in all specimens from the same uterus. It could be determined accurately from the biopsy specimen in every case except two in which the patients had been bleeding for more than 4 months.

2. In each case, variations in the degree of proliferative or secretory activity or in the extent of regression were observed. These tended to be distributed throughout the endometrium. In every case the general degree of activity, *i.e.*, mild or marked, and the presence of regressive changes, if any, could be determined accurately from the biopsy specimen. However, the latter did not in every case reveal the full extent of variation.

3. A 'mixed' picture was found in 6 cases. In each, the reaction was similar to that characteristic of the early secretory phase of the normal cycle. In each case, the variations were more or less uniformly distributed and were revealed by the biopsy specimen.

From the evidence cited, it may be concluded that the usual variation observed in the endometrial structure is variation within the limits of the characteristic reaction. However, variations in the type of reaction may occur. These tend to be uniformly distributed but patchy distribution or localized areas of variation have been observed in some cases of abnormal ovarian function. The endometrial biopsy specimen may or may not reveal the full extent of variation; it does afford reliable information concerning the type and general degree of development of the characteristic reaction.[1] Since this is the only information that it affords with certainty, it should not be interpreted in terms of the endometrium as a whole, but only in terms of ovarian function.

It must be borne in mind also that the endometrium is not an indicator of hormone production. It is an indicator of effective endocrine activity. As such, just what information does it afford?

The type of endometrial reaction affords information concerning the components of the ovarian secretion. But these cannot always be evaluated exactly. The preovulatory phase of the normal ovarian cycle is dominated by estrogen. However, the circulating estrogen is not all of one type. It is a mixture. Furthermore, small amounts of androgens are present, and evidence is accumulating to indicate that progesterone may be secreted before ovulation (49). The postovulatory phase is dominated by progesterone but whether or not this is the only component of the effective stimulus in the endometrium has not as yet been determined. It is known that there is a close relationship between the size and activity of corpora lutea and the level of estrogen in rodents (49).

The fact that the ovaries are secreting progesterone does not necessarily indicate that ovulation has occurred or that the endocrine activity of the ovaries is normal. The experimental evidence has been summarized by Allen (49). Clinical evidence indicates that enough progesterone may be elaborated from a corpus luteum cyst or from thecal luteinization to produce recognizable changes in the endometrium. Likewise, there is abundant clinical evidence that abnormal bleeding of functional origin may occur from an endometrium showing the secretory reaction (14, 27–39). We have produced this condition experimentally by injecting castrated monkeys with certain combinations of estrogen and progesterone (50, 1).

From the above facts, it is clear that the characteristic endometrial reaction indicates with certainty only the dominant component

[1] The specimen should be taken from the fundus or upper one-third of the corpus.

of the effective endocrine stimulus. Results of recent studies on the finer histology of the endometrium (15, 16, 51–55) give every indication that it will eventually be possible to establish criteria for obtaining more exact information. However, until such criteria have been established, it is preferable to define the endometrial picture in terms of the type and relative degree of activity rather than in terms of the hormonal stimulus.

The general stage of development of the endometrial reaction indicates the level of ovarian activity as compared with that characteristic of the normal fertile cycle. For example, well-marked endometrial proliferation indicates that the level of ovarian activity at the time the specimen was removed was that characteristic of the late preovulatory phase of the normal cycle. The endometrial reaction at the onset of bleeding indicates the maximum level of ovarian activity for the current cycle By correlating the endometrial histology with the menstrual history, the general level as compared with normal can be determined. But first we must know what is normal ovarian function.

It is becoming generally recognized that all of the following conditions must be satisfied before a diagnosis of normal ovarian function can be made: *a*) normal menstrual history, *b*) fully developed '28-day' endometrium at onset of bleeding, *c*) proven fertility, *d*) good nutritional and psychic status, *e*) absence of any constitutional or endocrine condition which might conceivably affect ovarian function.

If any of the above criteria are lacking, the normality of ovarian function is open to question. If there is a specific abnormality of menstruation (functional) or endometrial histology (*e.g.*, glandular cystic hyperplasia) a diagnosis of ovarian failure can be made. The findings of all investigators who have studied the endometrial changes associated with functional abnormalities of menstruation (27–44) and the results of our experimental studies (1–4) indicate that ovarian failure is a gradual process, affecting first the postovulatory phase of the cycle, progressing to complete absence of the postovulatory phase and finally to the postmenstrual level or lower. The condition may result from a variety of causes. It is manifested by a specific abnormality of either or both of the endometrial criteria of ovarian activity (cyclic histologic changes and menstrual bleeding). The degree of hypofunction is indicated by the endometrial structure at the onset of bleeding. For example, an endometrium showing histologic evidence of secretory activity at the onset of bleeding indicates that the ovaries are secreting progesterone or, in other words, that the maximum level of ovarian activity in this cycle is similar to that characteristic of the postovulatory phase of the normal cycle. The degree of hypofunction is, therefore, mild. An endometrium showing well-marked proliferation at the onset of menstruation indicates a more severe degree of ovarian hypofunction for this type of endometrium indicates that the maximum level of ovarian activity for the current cycle was that characteristic of the late preovulatory phase of the normal cycle. Glandular cystic hyperplasia indicates prolonged activity at approximately this level. A mild proliferative reaction in the endometrium at the onset of bleeding indicates that the level of ovarian activity for the current cycle was that characteristic of the early preovulatory phase of the normal cycle, or, in other words, that the degree of ovarian hypofunction is severe.

While we know the endometrial histology characteristic of ovarian hypofunction, and while much suggestive or direct evidence concerning the types of hormonal imbalance which produce them has been obtained, the general statement may be made that we do not know the exact nature of the hormonal imbalance which produces the given structure in the individual case. It is advisable, therefore, to avoid defining the endometrial structure in terms of the hormonal imbalance. It is our practice to define *a*) the endometrial reaction (pathologic diagnosis) in terms of the type and degree of activity, *e.g.*, mild proliferative, late secretory, and *b*) the degree of ovarian failure (clinical diagnosis)[2] in terms of the three levels of ovarian function that are clearly distinguishable on the basis of the type and general degree of development

[2] That is, clinical diagnosis of the degree of ovarian involvement. Primary and secondary ovarian failure cannot be diagnosed from the endometrium.

of the characteristic endometrial reaction as revealed by the biopsy specimen. According to our terminology, the clinical diagnosis of 'first degree ovarian failure' means that, at the onset of menstruation, the endometrium showed some evidence of having been stimulated by progesterone during the current cycle; 'second degree failure' means that the endometrium showed well-marked proliferation or glandular cystic hyperplasia at the onset of menstruation; 'third degree failure' means that the endometrium was of the castrate or postmenstrual type at the onset of menstruation.

The usual endometrial and ovarian correlations are well-known and need not be discussed here. However, it must be borne in mind that they are not necessarily the same in normal and abnormal ovarian function. It must also be borne in mind that any information which the endometrium affords regarding the ovarian structure or the ovulatory function is indirect, hence inferences drawn from endometrial findings concerning these aspects of ovarian function should be stated in terms of probabilities.

In conclusion, it is clear that in the present state of knowledge, the endometrium is the most valuable single indicator of ovarian activity in the human female and its histology the most informative single criterion. The endometrial biopsy specimen affords all of the significant information concerning ovarian function that can be obtained from endometrial histology at the present time. In view of the safety of the method and its advantages as compared with other means of obtaining endometrial tissue, the endometrial biopsy technic is a valuable diagnostic procedure and can be used for any purpose for which endometrial tissue is desired. The danger of possibly erroneous conclusions and unintended implications can be avoided if the following facts are borne in mind in interpreting the specimen. *a)* With respect to the state of the endometrium as a whole, the only thing the endometrial biopsy specimen reveals with certainty is the type and general stage of development of the characteristic reaction. *b)* With respect to ovarian function, the only thing that the endometrial biopsy specimen indicates with certainty is the general level of effective endocrine activity as compared with normal. *c)* Diagnoses should not be stated in terms of the hormonal stimulus. *d)* Inferences concerning ovarian structure and the ovulatory function should be stated in terms of probabilities.

REFERENCES

1. Burch, J. C., and D. Phelps: An experimental approach to the problem of mentrual disorders. *Ann. Surg.* 116: 604. 1942.
2. Burch, J. C., and D. Phelps: A general concept of the etiology of functional menstrual disturbances. *South. M. J.* 35: 150. 1942.
3. Burch, J. C., G. S. McClellan, C. D. Johnson and E. T. Ellison: The diagnosis and classification of menstrual disorders. *J. Am. Med. Assoc.* 108. 96. 1937.
4. Williams, C., D. Phelps and J. C. Burch: Observations on the effect of hypothyroidism on ovarian function in the guinea pig. *Endocrinology* 29: 373. 1941.
5. Klingler, H. H., and J. C. Burch: Suction in obtaining endometrial biopsies. *J. Am. Med. Assoc.* 99: 559. 1932.
6. Novak, E.: A suction-curet apparatus for endometrial biopsy. *J. Am. Med. Assoc.* 104: 1497. 1935.
7. Meigs, J. V.: Endometrial biopsy and the uterine index. *Am. J. Obst. & Gynec.* 38: 161. 1939.
8. Randall, L. M.: Endometrial biopsy of one hundred and fifty-six subjects. *Proc. Staff Mayo Clinic* 11: 58. 1936.
9. Lörincz, B.: Die Anwendung des Elektroaspirators in der Frauenheilkunde. *Münch. med. Wchnschr.* 81: 215. 1934.
10. Winkelstein, L. B.: Simplified suction for obtaining endometrial biopsies. *Am. J. Obst. & Gynec.* 42: 163. 1941.
11. Sharman, A., and H. L. Sheehan: Endometrial biopsy. *Brit. M. J.* 1: 965. 1937.
12. Tamis, A. B.: A modified instrument for biopsy of the endometrium. *Am. J. Obst. & Gynec.* 32: 505. 1936.
13. Lass, P. M., J. Smelser and R. Kurzrok: Studies relating to time of human ovulation. III. During lactation. *Endocrinology* 23: 39. 1938.
14. Israel, S. L., and C. Mazer: The safety and advantages of office curettage. An evaluation of the endometrial findings in 305 patients. *Am. J. Obst. & Gynec.* 36: 445. 1938.
15. Cleveland, R.: Cyclic changes in chromatin of the nuclei of the endometrium. *Surg., Gynec. & Obst.* 69: 18. 1939.
16. Cleveland, R.: Observations on the chromatin in the nuclei of endometrium from monkeys under experimental conditions. *Endocrinology* 27: 580. 1940.
17. Douglas, G. F.: A study of 107 cases of uterine bleeding with endometrial biopsies. *Am. J. Obst. & Gynec.* 41: 624. 1941.
18. Lörincz, B., and A. Davis: Intra-uterine aspiration. *Brit. M. J.* 1: 261. 1939.
19. Mishell, D. R.: The endometrial biopsy in early extrauterine pregnancy. *Am. J. Obst. & Gynec.* 41: 129. 1941.

20. Topkins, P.: The histologic appearance of the endometrium during lactation amenorrhea and its relationship to ovarian function. *Am. J. Obst. & Gynec.* 45: 48. 1943.
21. Palmer, A.: Basal body temperature in disorders of ovarian function and pregnancy. *Surg. Gynec. & Obst.* 75: 768. 1942.
22. Lyon, R. A.: Evaluation of dysmenorrhea by basal body temperature. *Surg. Gynec. & Obst.* 76: 729. 1943.
23. Howkins, J.: Biopsy of the endometrium. *Lancet* 2: 599. 1941.
24. Campbell, R. E., F. C. Lendrum and E. L. Sevringhaus: Endometrial histology and pathology as revealed by the biopsy method. *Surg., Gynec. & Obst.* 63: 724. 1936.
25. Sturgis S. H., and J. V. Meigs: Endometrial cycle and mechanism of normal menstruation. *Am. J. Surg.* 33: 369. 1936.
26. Rock, J.: The rôle of endometrial biopsy in diagnosis. *Am. J. Surg.* 48: 228, 1940.
27. Rock, J., and M. K. Bartlett: Biopsy studies of human endometrium. Criteria of dating and information about amenorrhea, menorrhagia and time of ovulation. *J. Am. Med. Assoc.* 108: 2022. 1937.
28. Herrell, W. E., and A. C. Broders: Histological studies of endometrium during various phases of menstrual cycle. *Surg. Gynec. & Obst.* 61: 751. 1935.
29. Griffith, L. S., and W. P. L. McBride: Clinical uses of endometrial biopsy. *J. Michigan Med. Soc.* 38: 1064. 1939.
30. Mishell, D. R., and L. Motyloff: The practical value of endometrial biopsies. *New York State J. Med.* 40: 928. 1940.
31. Wilson, L., and R. Kurzrok. Excessive uterine bleeding of functional origin. *Am. J. Obst. & Gynec.* 31: 911. 1936.
32. Hamblen, E. C.: The endometrium in "Endometrial Hyperplasia" after therapy. *Endocrinology* 20: 769. 1936.
33. Hamblen, E. C.: Endocrine Gynecology. Springfield, Illinois, Charles C Thomas. 1939.
34. Hamblen, E. C., R. L. Pullen and W. K. Cuyler: Clinical studies of thyrogonadal correlates: I. Basal metabolic rates and endometrial responses. *J. Clin. Endocrinology* 1: 523. 1941.
35. Kotz, J., and E. Parker: The clinical interpretation of the endometrial biopsy: report of three hundred cases. *Endocrinology* 24: 447. 1939.
36. Mason, L. W., W. C. Black and R. G. Gustavson: A correlation of endometrial histology with clinical symptoms. *Am. J. Obst. & Gynec.* 35: 189. 1938.
37. Anspach, B. M., and J. Hoffman: Endometrial findings in functional menstrual disorders. *Am. J. Obst. & Gynec.* 28: 473. 1934.
38. Jones, H. W.: Functional uterine bleeding with special reference to that associated with secretory endometrium. *Am. J. Obst. & Gynec.* 35: 64. 1938.
39. Keene, F. E., and F. L. Payne: Functional uterine bleeding. *South M. J.* 27: 108. 1934.
40. Payne, F. L.: The clinical significance of endometrial hyperplasia. *Am. J. Obst. & Gynec.* 34: 762. 1937.
41. Kurzrok, R., L. Wilson and M. A. Cassidy: The treatment of amenorrhea with large doses of estrogenic hormone. *Am. J. Obst. & Gynec.* 29: 771. 1935.
42. Lackner, J. E., L. Krohn and S. Soskins: The etiology and treatment of primary dysmenorrhea. A physiologic and clinical study. *Am. J. Obst. & Gynec.* 34: 248. 1937.
43. Rock, J., M. K. Bartlett and D. D. Matson: The incidence of anovulatory menstruation among patients of low fertility. *Am. J. Obst. & Gynec.* 37: 3. 1939.
44. Mazer, C., S. L. Israel and L. Kacher. Pseudomenstruation in the human female. *Surg. Gynec. & Obst.* 65: 30. 1937.
45. Barthelmez, G. W.: Histological studies on the menstruating mucous membrane of the human uterus. *Contrib. to Embryol.* 24: 143. 1933.
46. Traut, H. F., and A. Kuder: Irregular shedding and irregular ripening of the endometrium. *Surg., Gynec. & Obst.* 61: 145. 1935.
47. Wilson, L., and R. Kurzrok: Cystic endometrial changes in ovulatory cycles. The mixed endometrium. *Am. J. Obst. & Gynec.* 36: 302. 1938.
48. Phelps, D., C. A. Mella and J. C. Burch: An experimental evaluation of the technic of endometrial biopsy. *Anat. Rec.* 82: s. 437. 1942.
49. Allen, E.: Physiology of the ovaries. *J. Am. Med. Assoc.* 116: 405. 1941.
50. Cleveland, R.: Observations on hormone withdrawal bleeding in castrated macaques. *Endocrinology* 29: 343. 1941.
51. Black, J., O. S. Heyns and J. Gillman. The value of the basal fat in the human uterus as an indicator of optimum progesterone activity. *J. Clin. Endocrinology* 1: 547. 1941.
52. Rossman, I. Cyclic changes in the endometrial lipins of the rhesus monkey. *Am. J. Anat.* 69: 187. 1941.
53. Randall, L. M., and W. E. Herrell: Cystic changes in the endometrium. *Surg., Gynec. & Obst.* 65: 666. 1937.
54. Zondek, B., and L. Stein. Glycogen content of the human uterine mucosa glycopenia uteri. *Endocrinology* 27: 395. 1940.
55. Breipohl, W. Das Vorkommen von Glykogen bei der glandulär-cystischen Hyperplasie der Uterusschleimhaut und seine Bedeutung. *Zentralbl. f. Gynäk.* 60: 1481. 1936.

Abstracts of
CURRENT ENDOCRINE LITERATURE

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THYROID

MCLAUGHLIN, C. W., AND L. S. MCGOOGAN.

Hyperthyroidism complicating pregnancy. *Am. J. Obst. & Gynec.* 45: 591. 1943.

A series of 19 cases of hyperthyroidism complicating pregnancy is reported. It was found that the incidence of pregnancy in established thyroid disease is over three times as high as the incidence of hyperthyroidism developing during pregnancy. The thyrotoxicosis was definitely aggravated by the pregnancy in 74% of the series, increased in 21%, and unaffected in 5%. Toxemia occurred in 62.5% of the 8 patients admitted during the third trimester. Nothing other than conservative therapy is demanded in these cases. Eleven patients were treated conservatively with rest, Lugol's solution and sedatives. Nine of these deliveries were uneventful, in one section was done, and the eleventh is now in the eighth month of her pregnancy. Surgical treatment of the hyperthyroidism during pregnancy was done in 7 cases. Five of the patients successfully underwent subtotal thyroidectomy and subsequently delivered normal, live children. The other two were treated by staged polar ligation; one was delivered of a normal child at term whereas in the other, the baby was stillborn and macerated, the mother dying 14 days later. The other maternal death occurred in a woman with myocarditis and adenomatous goiter with mild hyperthyroidism.

It was concluded that the treatment of the patient with hyperthyroidism complicating pregnancy should be individualized. Surgery will be necessary more often in those with adenomatous goiter and hyperthyroidism than in those with primary exophthalmic goiter. Thyroidectomy is a safe surgical procedure and should be done at any stage if conservative treatment does not control the thyrotoxicosis.

There is a discussion of the experience of others with hyperthyroidism in pregnancy.—*E.C.H.*

MOEHLIG, R. C.

Hyperthyroidism. *Clinics* 1: 1115. 1943.

This article on thyroid hypersecretion discusses the subject particularly from the viewpoint of effects upon ectodermal and mesodermal tissues. Hyperactivity of the thyroid produces a degree of hyperplasia and hyperactivity of the ectodermal tissues, especially in the early stages of the disease. We may find exhaustion states follow excessive stimulation, and degenerative changes may result. An important part of clinical hyperthyroidism is hyperactivity of the skin function with intolerance to heat and increased electric conductivity. The hair follicles participate in the hyperactivity. The nails grow rapidly, presenting a spoon-shaped appearance, and may break off easily. Gynecomastia may be observed. Undue salivation may become annoying, with occasional swelling of the parotid glands. The connection of allergic states, such as hay fever, urticaria, eczema and asthma with the sympathetic-diencephalon-hypophyseal systems is probable. In youthful patients the dental enamel is well developed, resulting in beautiful teeth, but in chronic adult hyperthyroidism dental caries may result in rapid decay. The central nervous system presents characteristic symptoms. Occasionally there occurs a complicating psychosis. The digestive, circulatory, and vasomotor mechanisms may play a major rôle in the syndrome. The various related eye phenomena, the influence of hyperthyroidism on pregnancy, and the associated pituitary implications are discussed. Instances of thyreogenic osteoporosis and increased pigmentation are often found in hyperthyroidism. Enlargement of the lymphatic glands including the thymus and spleen is common. Lymphocytosis is a blood characteristic. The fat metabolism is increased so that weight loss is common. This is associated with a reduction in blood cholesterol. Changes in the gonads with menstrual abnormalities are a frequent accom-

paniment. The muscles are involved as evidenced by the marked weakness. Some observers believe that myasthenia gravis and exophthalmic goiter are distinctly related. Even the extraocular muscles may participate in this process, thus accounting for some of the eye signs in Graves' syndrome. —*I.B.*

NORA, E. D., AND N. FLAXMAN.

The heart in experimental thyrotoxicosis. *J. Lab. & Clin. Med.* 28: 797. 1943.

Normal rabbits were fed thyroid extract in sufficient doses to produce toxicity (from 2 to 16 grains daily of Armour's preparation). Five other groups of animals as follows were observed for comparison: thyroid fed and digifoline injected; thyroid and quinidine fed; cardio-inhibitory denervated; cardio-inhibitory denervated and digifoline injected; and cardio-inhibitory denervated and quinidine fed. The experimentally induced thyrotoxicosis caused parenchymmatous and fatty degeneration, cellular invasion, fraying and fragmentation, and fibrosis of the heart muscle. In animals with cardio-inhibitory nerves removed, similar changes, but not as marked, were brought about by cardiac overwork without an excess of thyroxin in the circulation. Quinidine had no influence on these or the tachycardia. While digitalis slowed the heart rate and decreased the degree of hypertrophy seen at autopsy, it did not materially alter the condition found in the thyrotoxic animal. The histologic changes seen in the heart of the thyrotoxic animal were not proportional to the alterations in the heart rate nor to the increased rate of blood flow per second.—*T.H.McG.*

REILLY, W. A.

Hypothyroidism—Latent symptoms. *Calif. and Western M.* 58: 73. 1943.

Hypothyroidism is rarely detected in its earlier stages and milder forms. The most common form occurs as a mild deficiency, progressing insidiously but persisting permanently. The degree of deficiency may be either progressive or cyclic characterized by exacerbations rather than remissions. Therapeutic results are best when treatment is begun early. Myxedema is rare in the early stages of hypothyroidism. Diagnosis of early cases is often difficult. Not even a low basal metabolic rate is pathognomonic and a normal metabolic rate does not necessarily rule out an early thyroid deficiency. Clinical analysis is more dependable than laboratory findings. Indeed, the mild or moderate hypothyroid patient may present nervousness to complicate the picture. This is not uncommonly observed in tall, thin adolescent girls in whom thyroid extract may relieve nervousness, improve weight and expedite maturity.—*I.B.*